FACULTY OF SCIENCES

Towards the synthesis of analogs of (+)-peloruside A, a natural product with promising biological properties

Dries Van den Bossche

Spring 2017

Promotor:
Prof. Dr. Johan Van der Eycken

A dissertation submitted to Ghent University in partial fulfilment of the requirements for the degree of Doctor in Sciences: Chemistry

GHENT UNIVERSITY

AGENTSCHAP INNOVEREN & ONDERNEMEN

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At the beginning of this dissertation it is appropriate to show my gratitude to those who made this work possible.

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Thank you, colleagues at WE07, not only from my own group, but also from the other research groups, for the scientific support and for making S.4 a nice place to work. In particular, I would like to thank Nick Jacobs, my lab mate for the majority of my PhD.

A massive thank you, to my family and my friends. Thank you for the continuous support, for the fun and the laughter, for being there for me. I will not name all of you, but I hope that those involved have received enough appreciation along the way. Now let us close down this chapter together and move on to new endeavours.

Dries Ghent, May 12th 2017

Contents

"Nature creates nothing without a purpose"

Aristotle

1

Introduction

In this chapter, our interest in natural products is explained. Also the target of choice, (+)-peloruside A is introduced as well as its interaction with biological systems.

1.1 The importance of natural products

Nature has been a source of medicinal products since time immemorial.[1–4] The first records of sophisticated traditional medicine systems were carved on clay tablets in Mesopotamia and date back to about 2600 B.C. They described, among other things, the use of oils from different species (e.g. opium poppy, *Papaver somniferum*) to treat a variety of disorders, ranging from coughs to parasitic infections and inflammation. Many of these are still used today. Also in ancient Egypt, proof of early medicine was found. The best known pharmaceutical record is the Ebers Papyrus, from 1500 B.C., which describes more than 700 'drugs', mainly plants, but also animals and minerals, and how to administer them: at that time, beer, milk, wine and honey were commonly used vehicles. The first records of Chinese and Indian civilizations describing the use of a wide variety of active (plant) ingredients (drugs) date both from about 1100 B.C. Oral tradition probably dates back way longer.[2]

In the ancient Western world, the Greeks and Romans contributed substantially to the rational development of the use of herbal drugs. Theophrastus, a disciple of Aristotle (around 300 B.C.), dealt with the medicinal use of plants in his 'Enquiry into plants' (*Peri phyton historia*). Later, the Greek physician Dioscorides (100 A.D.) travelled with the Roman armies in search of medicinal substances from all over the Roman Empire. His work resulted in 'On Medicinal Material' (*De Materia Medica*), an encyclopedia of about 600 plants, and a description of which medicines can be obtained from them, when to use them, and in which quantities. The Greek physician Galen (129-216 A.D.) published over 30 books on pharmacy and medicine, and is well known for his complex prescriptions and formulas used in compounding drugs, sometimes containing dozens of ingredients.[1]

Besides the monasteries in Western countries, it were especially the Arabs who

were responsible for the preservation of the Greco-Roman expertise, during the Middle Ages. Even more, they expanded this knowledge to include the use of their own resources, together with those of Chinese and Indian culture, which were unknown to the West until then.[3]

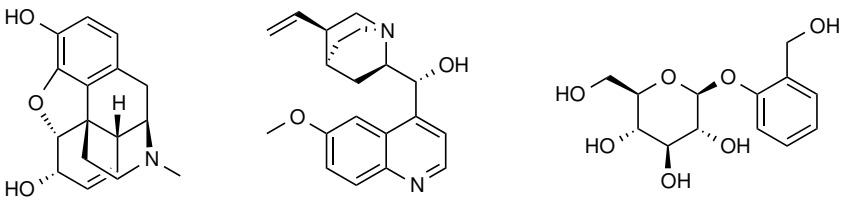
During the Renaissance, interest in medicinal properties of natural products revived in the West. Paracelsus, a German-Swiss physician and alchemist, was the first to declare a link between pure chemical compounds in substances and their effect as drug.[2]

> *"Quas enim oculis herbas cernimus, id non est Medicina. Item quas gemmas, quasve arbores videmus, non est id Medicina recta ac perfecta. Oculi enim saltem partem immundiorem ac rudem materiam vident, quae a recta Medicina nondum segregata est, et in qua impurior pars adhuc occultatur. Quid igitur? Impurior pars prius purganda est et abicienda, et postea Medicina apparebit."*
>
> Paracelsus, *Labyrinthus medicorum errantium*

> "The herbs, minerals and trees we see, are not the medicine. We only see a crude product, where the impurities are not yet separated from the actual active medicine. What do we have to do then? We must first purify this crude product; get rid of the impurities and then, the medicine will appear."

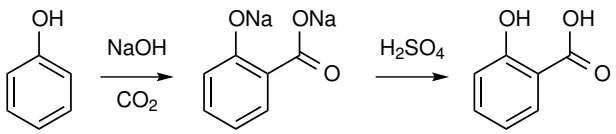
It was only until the beginning of the 19th century, that these active substances were isolated in pure form. The use of poppy juice as a painkiller was described already in the first Mesopotamian records, but the active substance, morphine (**1.1**), was isolated only in 1804. Also the use of the bark of the cinchona tree in treating malaria is a historic example of medical treatment from natural sources. It was readily used by the Indians in the Andes and in the 17th century introduced in Europe. Because of the bitterness of the cinchona powder, the British mixed it with sugar and water, and thus protected themselves from malaria during the

occupation of India, by drinking tonic (and gin).[2] The active component, quinine (**1.2**), was first isolated in 1820. Besides the use of the bark of the (Peruvian) cinchona tree, it was discovered early on (1758) that the extract from the bark of the willow tree also had a positive effect in the treatment of malaria. Rather than targeting the cause of malaria, it relieved the symptoms. The willow tree had been used in ancient civilizations, in the treatment of fever, pain and inflammation. Its active ingredient, salicin (**1.3**), was obtained in a pure form in 1829, and seemed to be comprised of a sugar (D-glucose) and salicyl alcohol.[5,6] At this point, only the chemical composition was known, not the structural formula, as concepts like aromaticity or covalent bonds were only introduced later (respectively, by Kekule and by Pauling). Oxidation of salicyl alcohol yielded salicylic acid **1.4**, which was found before in the leaves of wintergreen plants, and which was also used as pain reliever. The German Hermann Kolbe came up with a process of synthesizing this salicylic acid from sodium phenolate and carbon dioxide in 1859 (scheme 1.1). To avoid side effects of the use of this drug, particularly gastric irritation, the acidity of salicylic acid was lowered by acetylating it, resulting in aspirin, synthesized on an industrial scale in 1899 by Bayer and still one of the most popular drugs.



1.1 **1.2** **1.3**

Figure 1.1



1.4

Scheme 1.1: Kolbe's synthesis of salicylic acid **1.4**

Not only plants, but also microorganisms (bacteria and fungi) and marine organisms are conventional sources for natural products. Microorganisms have always been part of human life. Be it as food (yoghourt), for the preparation of alcoholic beverages (yeasts), but also as medication. The discovery of penicillin from the fungus *Penicillium notatum* by Fleming in 1929 and especially the use of this as a therapeutic in the 1940's were important milestones. They preluded the 'Golden Age of Antibiotics' and resulted in extensive investigation of Nature as a source of novel bioactive agents.

Marine organisms on the other hand, do not have a significant history of use in traditional medicine. This changed with the development of diving equipment, some 50 years ago. Given the fact that 70% of earth's surface is covered by water, pharmaceutical companies realized that the oceans possess a vast amount of novel, structurally diverse, compounds. Therefore, the marine environment has been increasingly explored as a source of bioactive compounds.[7]

Technological advances in instrumentation and structure elucidation techniques improved the identification process of novel bioactive natural products. However, in spite of these technological advances along the years, the screening of extracts and isolation of the active component were still time-consuming. Therefore, in the beginning of the nineties, the focus shifted somewhat away from natural products. The advent of automated high-throughput screening (HTS) had caused an acceleration in biological testing, and as traditional extract-based screening could not keep up with this speed, combinatorial chemistry was promoted as a better approach to create "drug-like" compounds for HTS.

From 1997 on, Newman and Cragg reviewed the sources of new chemical entities (NCEs), approved by the US Food and Drug Administration (FDA), the European Medicine Agence (EMA) and similar institutions.[8–10] It has been updated regularly and is currently in its 4th edition, covering a time period from 1981 to 2010.[11] They classified the NCE's in different categories, based on their origin: natural products as such (N), substances which are derived from natural products, usually a semi-synthetic modification (ND), synthetic compounds without natural product conception (S), synthetic compounds of which the pharmacophore is de-

rived from a natural product (S*), and natural product botanicals, a class which covers "defined mixtures" of botanicals (NB). They also use the subclass /NM to indicate if a synthetic compound competes for a natural product target. To clarify this classification, an example from each class belonging to the field of cancer treatment will be given (figure 1.2).

Perhaps the most known natural product (N) in cancer treatment is paclitaxel (**1.5**) (Taxol® by Bristol-Meyers Squibb), which is isolated from the bark of *Taxus Brevifolia*, the (rare) Pacific yew tree.[12] In an effort to cope with the limited bioavailability of paclitaxel, researchers developed the semi-synthetic analog (ND) docetaxel (**1.6**) (Taxotere®, Sanofi-Aventis), which is made starting from a readily available precursor, 10-deacetyl baccatin III (**1.7**), from the more common European yew tree. Carboplatin (**1.8**) is a totally synthetic molecule (S) which causes DNA crosslinking, which inhibits in turn DNA repair and/or synthesis in cancer cells. The non-steroidal bicalutamide (**1.9**) on the other hand is also a purely synthetic molecule, but is appointed the subclass 'natural product mimic' (S/NM) as it competes with the natural ligand testosterone (**1.10**) for binding onto the androgen receptor.[13] Decitabine (**1.11**) is a synthetic cytidine (**1.12**) analog (S*), which is incorporated in DNA strands upon which this is not recognized anymore, and therefore, DNA methyltransferase is inhibited.[14] Bexarotene (**1.13**) is a formally synthetic compound, but chemically related to vitamin A.[15] It also competes with the natural 9-cis-retinoic acid (**1.14**) for binding on the retinoid X receptor, thus it belongs to the subclass of the natural product mimics (S*/NM).

Compounds from biological sources, such as proteins or monoclonal antibodies (B) and vaccines (V) are also discussed in the reviews, but are not considered here.

From the analysis, a few conclusions can be drawn (figure 1.3). First, while 66% of the 1073 approved small molecule NCE's are formally synthetic (containing S or S* in their nomenclature), only 36% of them is truly synthetic. The other 30% either corresponds to compounds containing a natural product-derived pharmacophore (S*) or to compounds which are modeled on, or compete for a natural product inhibitor of the molecular target (NM subclass). When looking at the class of anticancer drugs, the numbers drop even lower to only 20% of the small

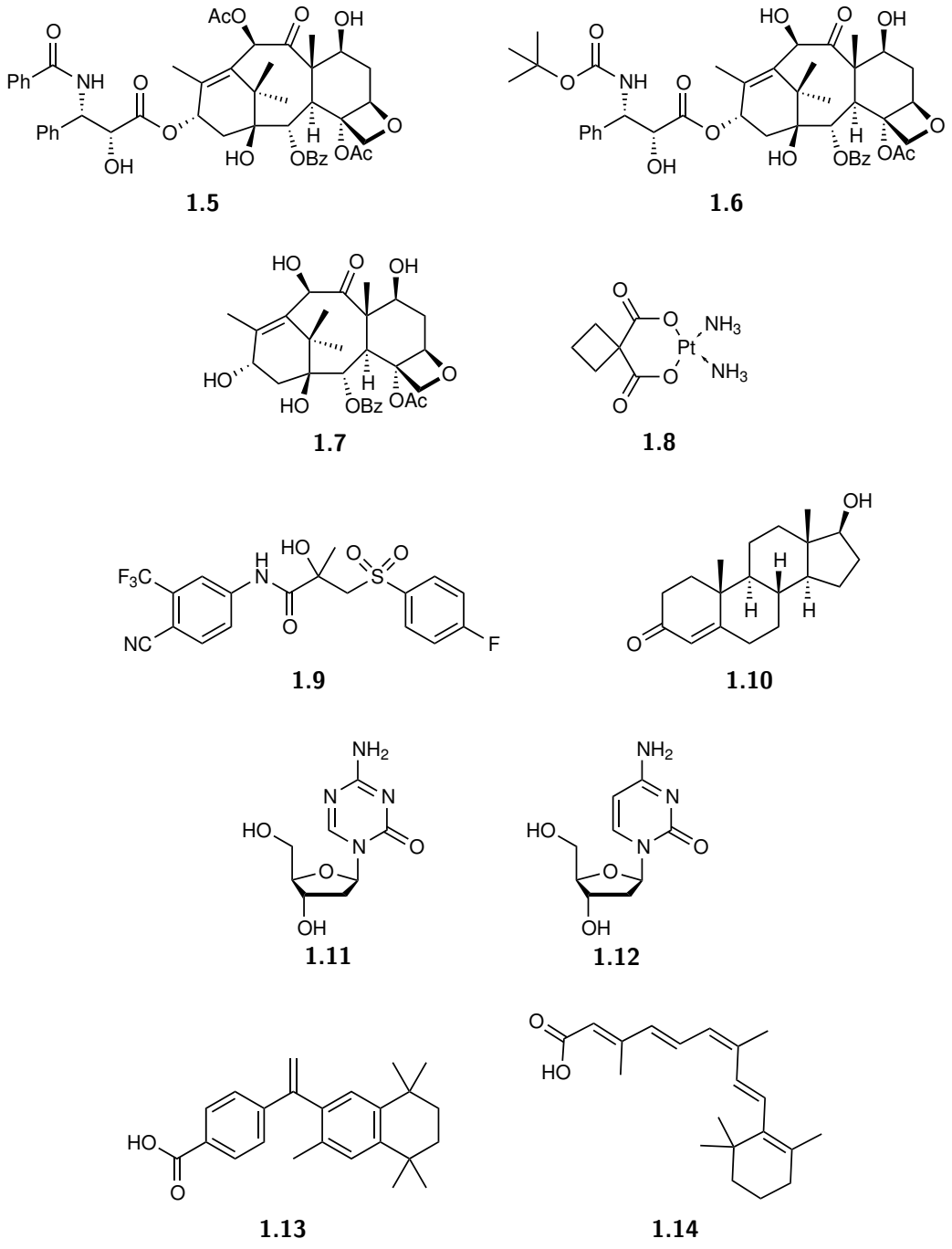


Figure 1.2: Selected examples from each class of NCE's, according to Newman and Cragg

molecule drugs being purely synthetic (S). Even more, out of the seven in 2010 approved antitumor agents, six of them were small molecules, of which one was a natural product as such (N), and four are derived from natural products (ND). This really shows the importance of exploring nature as source of new drugs.

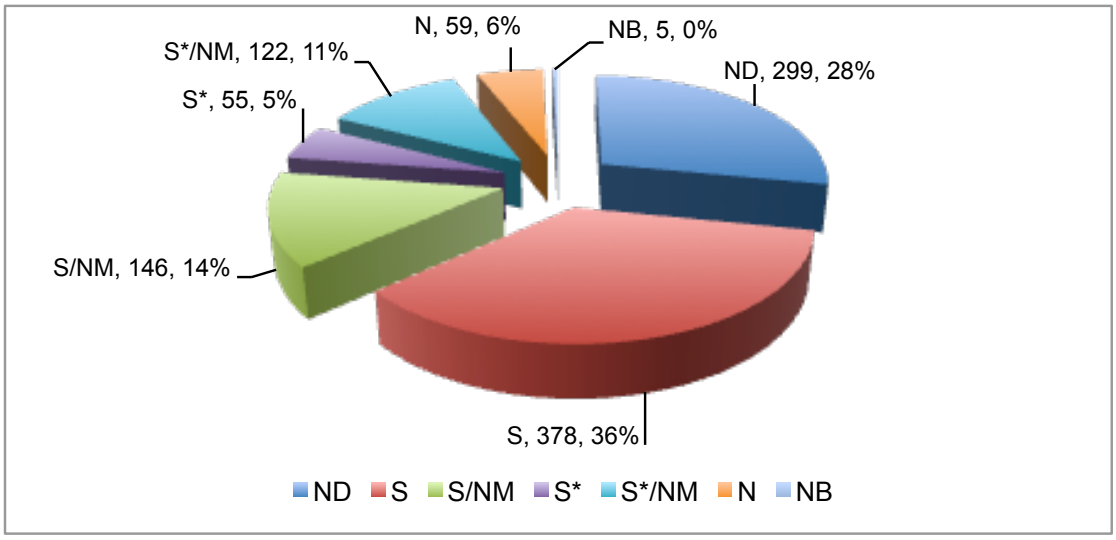


Figure 1.3: Source of small molecule approved drugs from 1980 to 2010. Reprinted with permission from[11] Copyright 2012, American Chemical Society.

Secondly, as reflected from the numbers and figures in the reviews, it is clear there is a decline in output of R&D programs from pharmaceutical companies, from the late eighties on (figure 1.4). A number of factors can be attributed for this downward trend: the mounting costs of drug discovery, FDA's over-caution in the drug approval process, and the disruption of laboratory activities because of the merging of several companies.[16] According to several researchers however, it is significant that the downward trend in output has occurred during a period of declining interest in natural products, in favor of reliance on new chemical techniques such as combinatorial chemistry, because of the compatibility of these with HTS approaches.

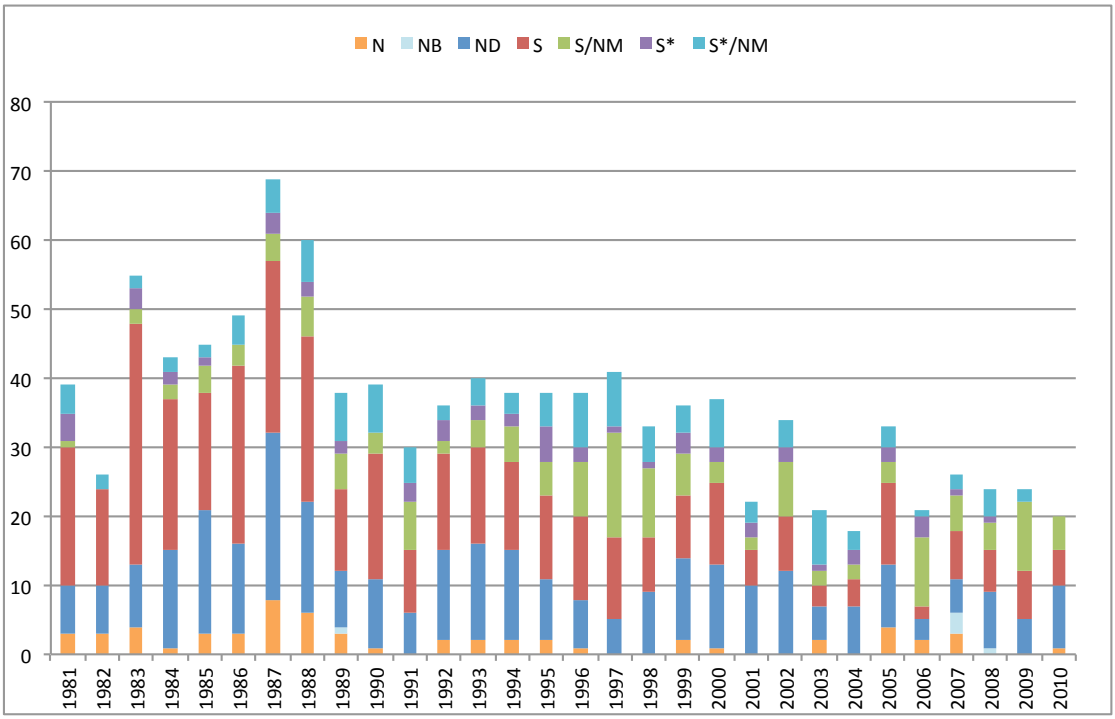
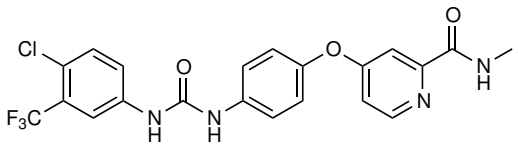


Figure 1.4: Source of small molecule approved drugs from 1980 to 2010, by year. Reprinted with permission from[11] Copyright 2012, American Chemical Society.

Indeed, as the emphasis was mainly on the synthesis of large libraries of small compounds, lacking molecular complexity and possessing a lot of flexibility, the expected output in new chemical entitities was not realised.[17,18] In fact, only one *de novo* NCE resulting from combinatorial chemistry has been approved by the FDA so far, which is the kinase inhibitor sorafenib (Nexavar®, by Bayer) (**1.15**).



1.15

Figure 1.5: Sorafenib

Because apparently combinatorial chemistry did not live up to the expectations,

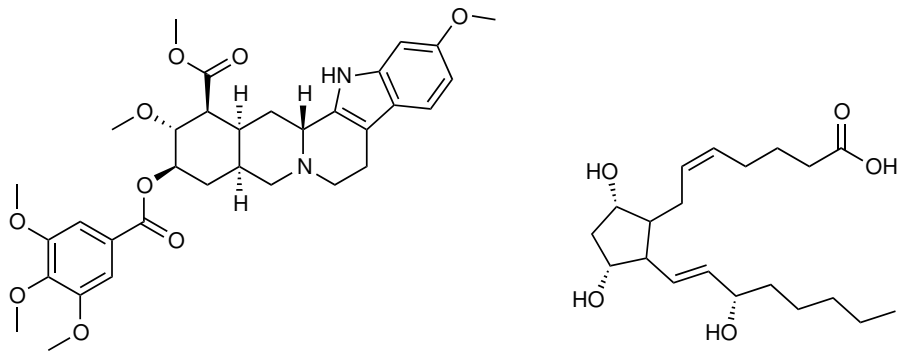
there was an evolution at the end of the nineties. The size of the libraries was scaled down from tens of thousands or even millions of compounds towards tens to hundreds of compounds. At the same time, the molecular complexity of the compounds was increased, introducing bicyclic structures and chirality, resembling more and more natural products. The introduction of these more complex, three-dimensional natural product-like structures are thought to create better chances of interacting with biological targets. This concept is also known as diversity-oriented synthesis (DOS), formally introduced by Schreiber in 1998.[19–22]

A variant of this approach, is biology-oriented synthesis (BIOS), introduced by Waldmann, where libraries are created by combining structural features of the basic carbon skeleton of natural products and tested against clustered proteins with a similar three-dimensional space around the binding pocket.[23,24]

As evidenced by this shift in combinatorial chemistry research, natural products have continued to play a crucial role in the drug discovery process as they provide a very valuable and vast pool for the discovery of templates and drug candidates. Furthermore they are suitable for further optimization by synthetic means because the chemical complexity of natural products is higher than structures from any other source. In that respect, the discovery of natural products has been a driver in the evolution of organic chemistry. As E. J. Corey put it: "*natural products are engines of the development of organic chemistry and links to the domain of biology.*"[25]

The complexity and molecular diversity indeed have boosted the development of organic chemistry. In the 1940's to 1960's, R. B. Woodward succeeded in synthesizing dozens of diverse structures of unprecedented complexity, among them quinine[26,26] (**1.2**), reserpine[27] (**1.16**) and prostaglandin $F_{2\alpha}$[28](**1.17**). These achievements are particularly admirable as many of the now available purification or spectroscopic techniques did not exist yet at that time.

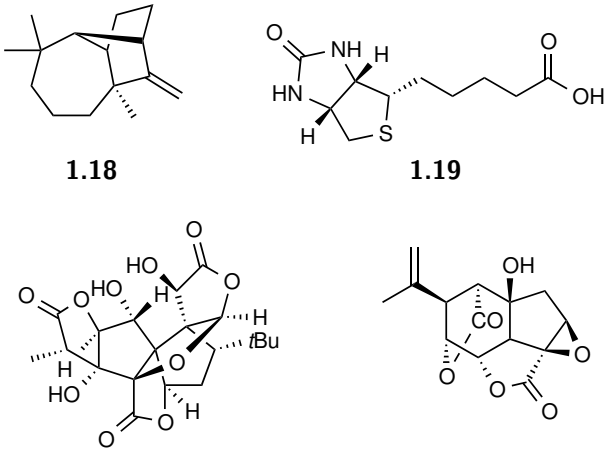
With the advent of new analytical techniques, there was a surge in the identification of new natural products, which demanded for a more systematic approach in designing a synthetic strategy. An answer to this demand was provided by E.



1.16 **1.17**

Figure 1.6: Selected examples from natural products, synthesized by Woodward

J. Corey with the introduction of retrosynthetic analysis in 1961, for the synthesis of longifolene[29] (**1.18**, figure 1.7). In the following 30 years, Corey managed to synthesize hundreds of natural products, including biotin[30](**1.19**), ginkgolide B[31] (**1.20**), picrotoxinin[32] (**1.21**), ... This resulted in the development of new synthetic methods, mechanistic proposals and asymmetric syntheses and led to important contributions to the field of biology and medicine.



1.18 **1.19**

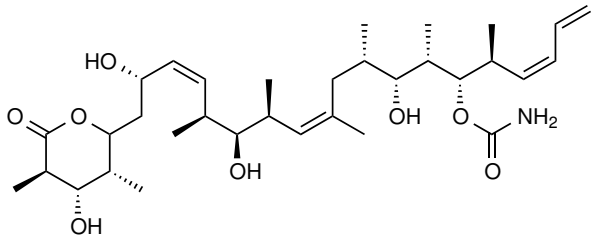
1.20 **1.21**

Figure 1.7: Selected examples from natural products, synthesized by Corey

The importance of total synthesis of natural products is evidenced as a Nobel Prize in Chemistry was awarded to both Woodward (1965) '*for his outstanding*

achievements in the art of organic synthesis' and to Corey (1990) '*for his development of the theory and methodology of organic synthesis*'. The efforts and accomplishments of these two brilliant chemists have inspired and stimulated many others to focus on the art and science of total synthesis.[33,34]

Total synthesis of natural products in many cases is appealed to for the elucidation, confirmation or revision of a complex structure, especially when the absolute configuration is unknown. On the other hand, total synthesis is often used as a link to drug development programs, to deal with the supply of natural products. When these are difficult to isolate in sufficient amounts, total synthesis is called upon to deliver the necessary amounts to do (pre)clinical testing and later to bring the drug to the market. A beautiful example of the above described use of natural products is the story of discodermolide (**1.22**, figure 1.8). Discodermolide is a natural product which showed great potency as antitumor compound, but it was isolated only in small amounts out of a sea sponge which is very rare. First, the absolute configuration of the product was established through the synthesis of both enantiomers by Schreiber.[35] Since then, different research groups were able to improve yields, efficiency and economy.[36–38] These methodologies were used by Novartis to produce multigram amounts of the compound and bring it to the clinic.[39–43] Unfortunately, the results of the clinical trials showed a lack of response and an increased toxicity, so the program was stopped.



1.22

Figure 1.8: Discodermolide

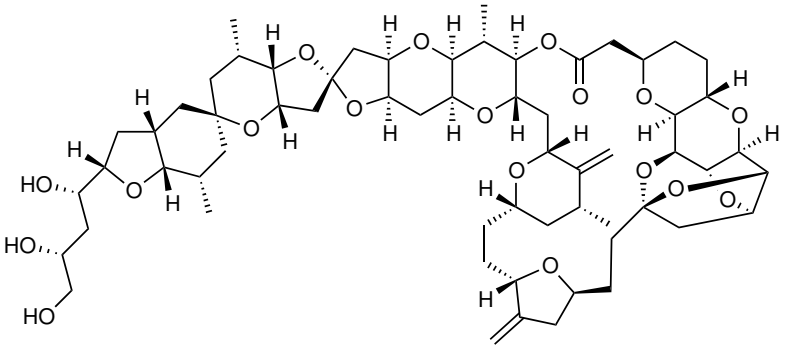
The story of discodermolide also proved something else: while natural products often exhibit highly potent and selective bioactivity through interaction with a

certain target, they are originally produced in their ecosystem for uses other than we seek or need. Thus, natural products as such are not optimized to possess the characteristics which are desired in a clinically useful drug. Also, the structural diversity of natural products is limited by the available biosynthetic pathways of the host organisms. Hence, it can be advantageous to synthesize analogs of the natural product. In that way, the accessible structural diversity becomes immense.

When the natural product is easily accessible, diversification is probably the simplest approach: functional group transformations can easily provide a lot of analogs. However, one should keep in mind, that some desired transformations cannot be performed as there can be incompatibilities with other functional groups that are present in the molecule. Sometimes, as is the case for paclitaxel, there is a readily available precursor, which can then be modified to gain access to a new variety of analogs through semi-synthesis.

Another option is to focus on the pharmacophore of the natural product: the substructural part of the molecule that bears the essential features necessary for activity. Synthesizing an advanced intermediate that lacks the unnecessary complexity, results in simplified analogs with a similar or even better activity than the original natural product. This strategy is named diverted total synthesis by Danishefsky, and is often a consequence of target oriented total synthesis.[44,45] A notable example is that of halichondrin B (**1.23**, figure 1.9), where total synthesis studies revealed that the right hand half of the molecule is responsible for almost all of the activity. This resulted in the synthesis of the simplified analog eribulin (Halaven®, **1.24**), which was approved by the FDA in 2010, and is now produced in a totally synthetic way.[46–48]

Closely related to this is the concept of function oriented synthesis (FOS), introduced by Wender. The central principle of FOS is: "*that the function of a biologically active lead structure can be emulated, tuned or even improved by replacement with simpler scaffolds designed to incorporate the activity-determining structural features (or their equivalent) of the lead compound.*"[49,50] By defining the minimum set of features needed for a desired activity, it is possible to incorporate, through design, the required functionalities into more accessible and effective



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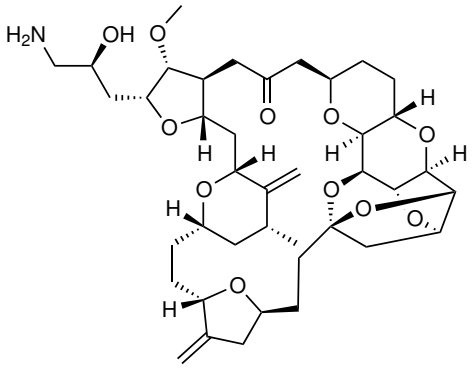


1.24

Figure 1.9: Halichondrin **1.23** and the simplified analog Eribulin**1.24**

agents. In this context, the series of bryostatin analogs Wender came up with, is noteworthy. Bryostatin (**1.25**, figure 1.10) is a natural product that binds to protein kinase C (PKC), which is responsible for a whole array of downstream signaling events. Therefore, bryostatin is now in clinical trials for the treatment of cancer and Alzheimer's disease. Through computer-guided comparison of the known PKC ligands, Wender proposed that the southern half of bryostatin is responsible for binding, whereas the northern half is responsible for keeping the southern half in the correct conformation. This resulted in a first generation of a simplified, but still very potent analog with a simplified northern half (spacer domain) (**1.26**). Recently, based on further in silico studies, they came up with a second generation analog, where the spacer domain is replaced by a salicylate

(**1.27**).[51] A simplification which resulted in a decreased number of steps, at the expense of only a modest decrease in binding affinity (18 nM for salicylate vs. 1.1 nM for bryostatin).

This dissertation is also situated in the field of function oriented synthesis, the natural product of interest being (+)-peloruside A.

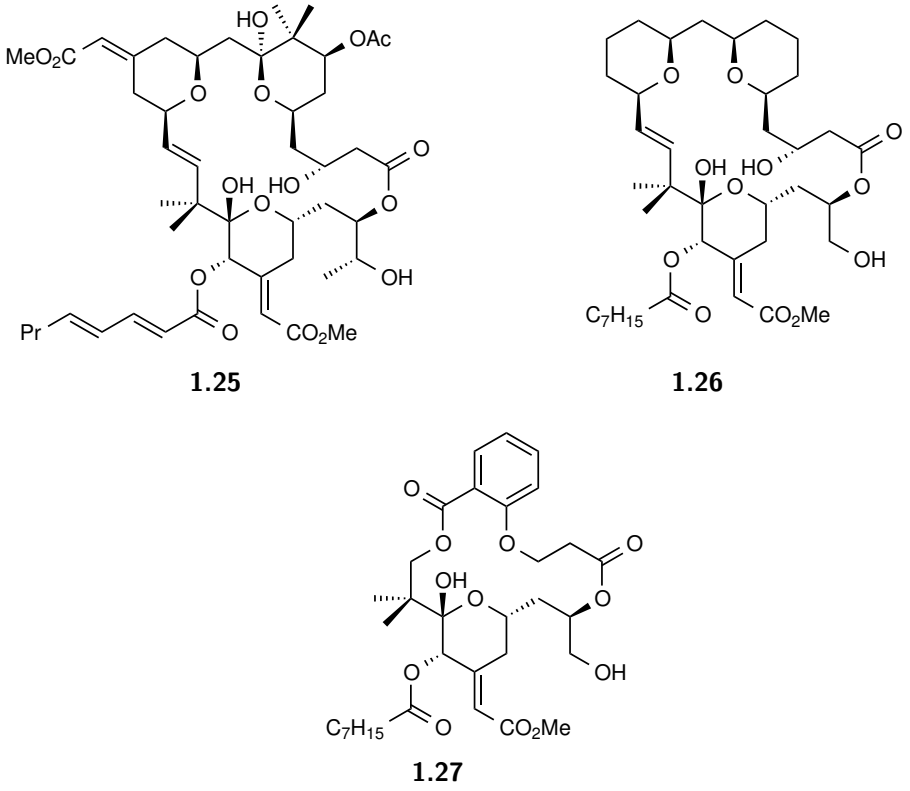


Figure 1.10: Different generations of Bryostatin analogs

1.2 (+)-Peloruside A

1.2.1 Discovery

(+)-Peloruside A (**1.28**, figure 1.11) was discovered in 1999 by Northcote, West and Battershill.[52] They isolated the natural product from the sea sponge *Mycale hentscheli*, together with three other compounds: (+)- mycalamide A (**1.29**) and pateamine A (**1.30**) and B (**1.31**). These are all secondary metabolites that show cytotoxic activity: the sponge produces these toxins to prevent growth of organisms that compete for food and space. In this context, secondary metabolites do not have a primary function directly involved in the normal growth, development or reproduction of a species, but indirectly assist in survival during evolution.

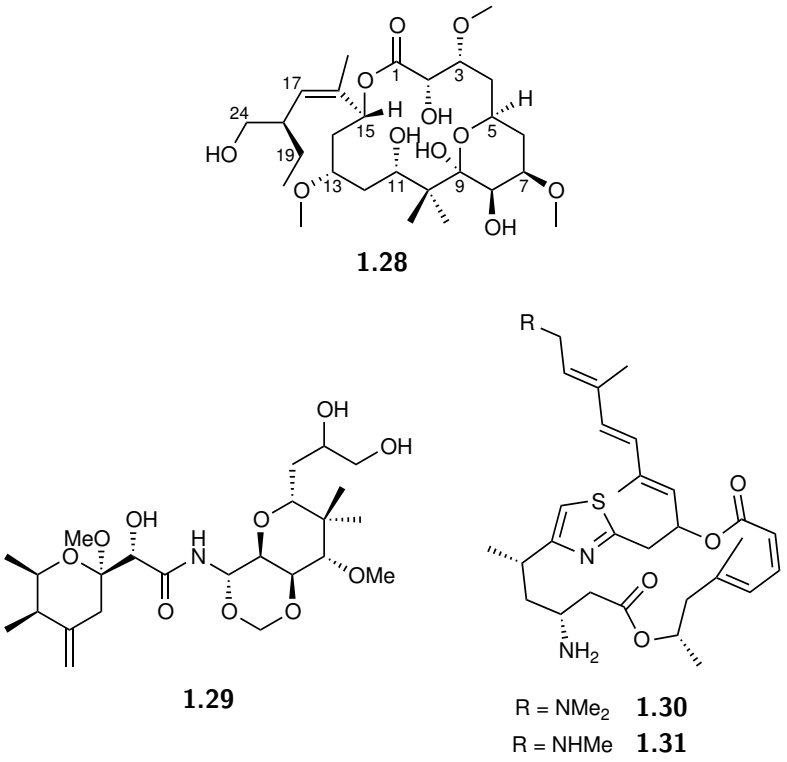


Figure 1.11: Secondary metabolites of the sea sponge *Mycale hentscheli*

Sponge specimens of *Mycale hentscheli* were collected at a depth of 7 to 15 me-

ters in a specific place in New Zealand: the Pelorus sound. Because the structures of the pateamines and mycalamide were already known from specimens collected at other places, Northcote, West and Battershill named the new compound peloruside A, after the original location of presence. It was observed that only specimens collected at the deeper range of the sponge population contained detectable amounts of peloruside A.

The original process to obtain pure compound starting from wet sponge is very laborious and described in figure 1.12. The prevalence of peloruside in the sea sponge is minimal as only 3 mg was isolated out of 170 g of wet sponge.

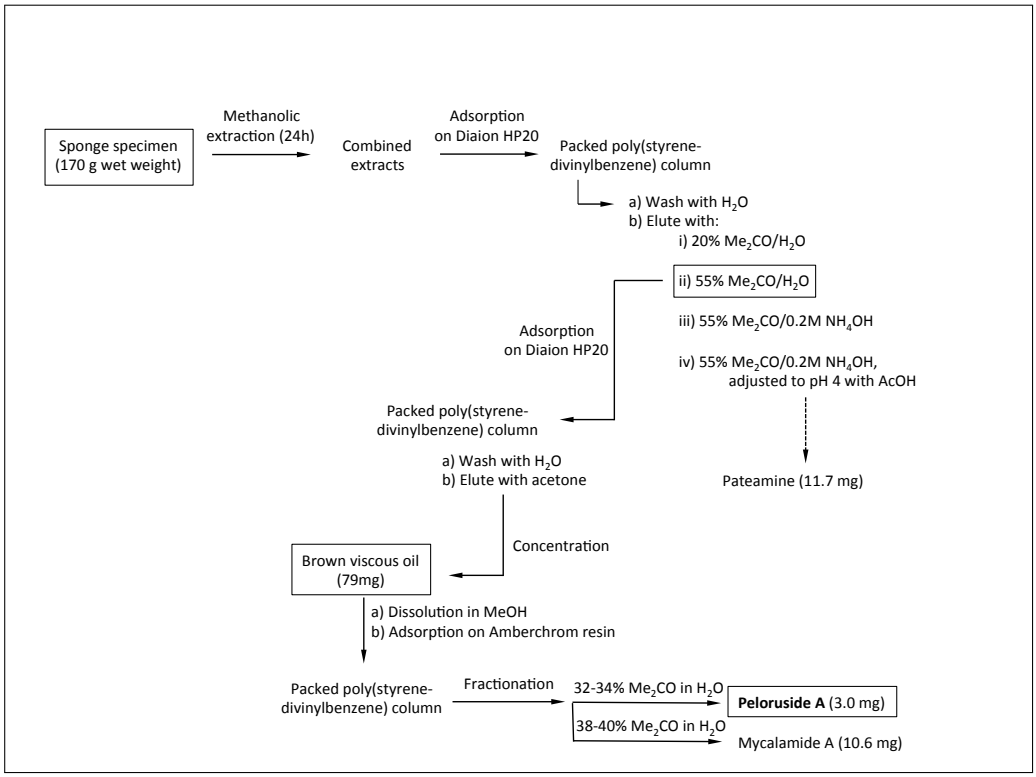


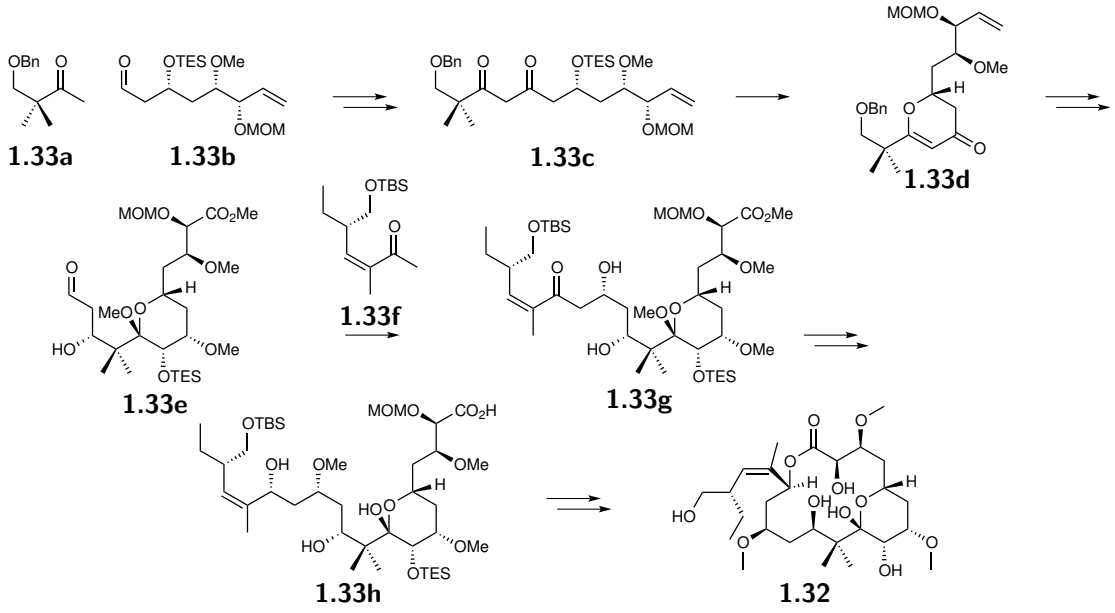
Figure 1.12: The isolation process of peloruside A as described by Northcote *et al.*

Initially, Northcote et al. proposed the strucure of peloruside to be a 16-membered, polyoxygenated macrolide, containing a pyranose ring, a trisubstituted olefin possessing the Z-geometry and ten stereogenic centers. The connectivity of

the basic skeleton was established via NMR, using COSY, TOCSY and HMBC experiments, whereas the relative configuration of the stereocenters was proven using NOE correlations and vicinal couplings. However, because peloruside appears as a colorless oil, it was not possible to obtain a crystal structure, and thus only the relative configuration of these stereocenters could be determined. Upon measurement of a positive sign of optical rotation (measured as solution in CH_2Cl_2), the compound was named in full (+)-peloruside A.

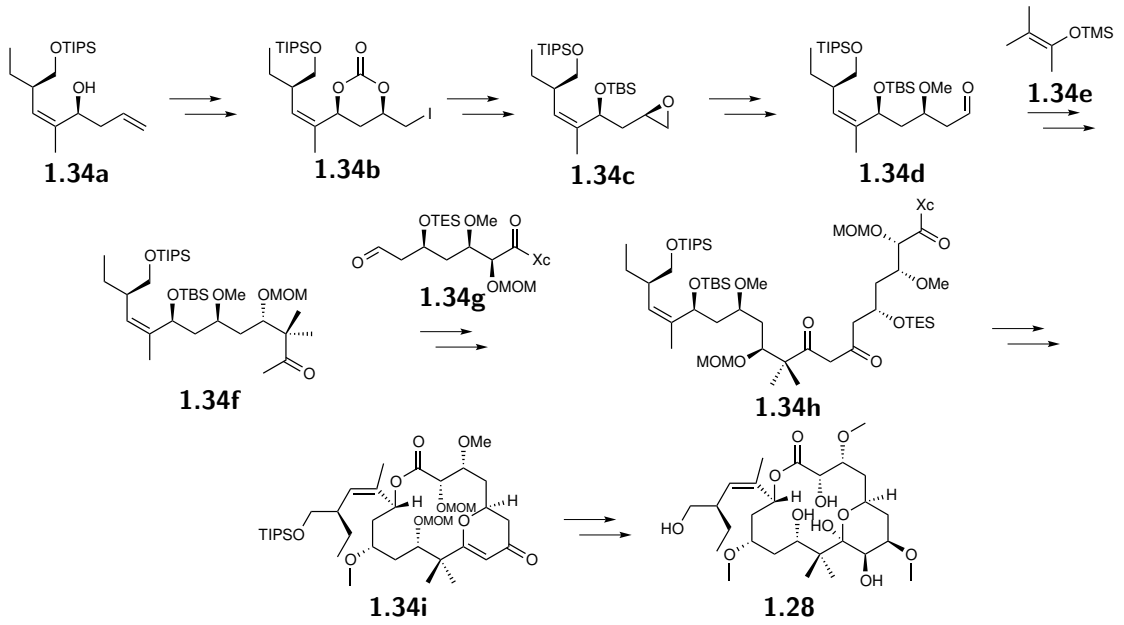
1.2.2 Synthesis

In 2003, De Brabander *et al.* published the first total synthesis of peloruside.[53] This synthesis was of paramount importance for the determination of the absolute configuration, as it was not yet known at that time. The originally synthesized compound turned out to be the enantiomer (-)-peloruside A (**1.32**) (scheme 1.2), possessing a negative sign of optical rotation and showing no effect on the growth of tumor cells *in vitro*. Later, in a patent, De Brabander also described the synthesis of the natural product (+)-peloruside A.[54] In the synthesis of (-)-peloruside A, methyl ketone **1.33a** is coupled in an aldol reaction with aldehyde **1.33b**, followed by oxidation, to form diketone **1.33c**, which forms dihydropyranone **1.33d** after deprotection. This fragment is further elaborated towards the advanced aldehyde **1.33e**, which is coupled with methyl ketone **1.33f** in another aldol reaction to form **1.33g**. After the enantioselective reduction and deprotection steps, *seco* acid **1.33h** is formed, which undergoes Mitsunobu-type macrolactonization (69% yield), resulting in (-)-*ent*-peloruside A (**1.32**) after final deprotection.



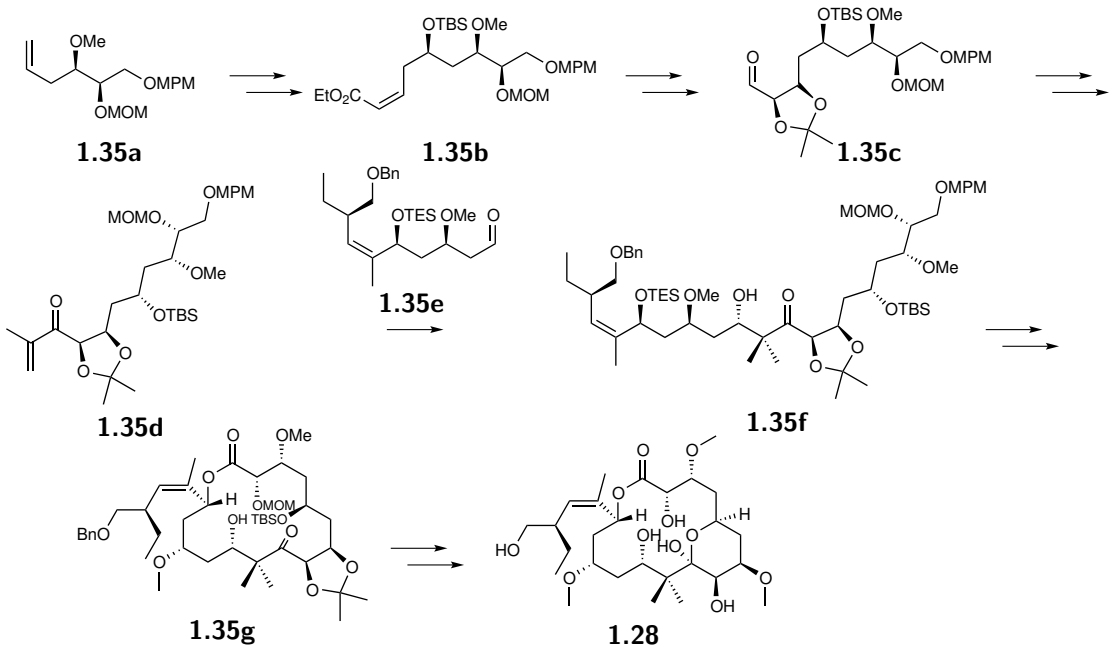
Scheme 1.2: Synthesis of (-)-*ent*-peloruside A by De Brabander *et al.* (2003) (LLS: 31 steps)

In 2005, Taylor *et al.* published a new synthesis of (+)-peloruside A, relying on alternative aldol couplings (scheme 1.3).[55] Homoallylic alcohol **1.34a** is Boc-protected, and consecutively transformed to iodocarbonate **1.34b**. This is converted to epoxide **1.34c**, which undergoes nucleophilic attack by the anion of 1,3-dithiane to form aldehyde **1.34d**. The carbon skeleton of this fragment is elongated by Mukaiyama-type aldol reaction with silyl ether **1.34e**, to form advanced methyl ketone **1.34f**. This is coupled with aldehyde **1.34g**, which was obtained, making use of an oxazolidinone as chiral auxiliary (Xc). Consecutive oxidation delivers diketone **1.34h**, which is transformed into dihydropyranone-containing macrolactone **1.34i** by applying the necessary deprotections and Yamaguchi macrolactonisation (51% yield). After ring closure, the dihydropyranone ring is converted to the pyranose ring using the same conditions De Brabander used in his synthesis.



Scheme 1.3: Synthesis of (+)-peloruside A by Taylor *et al.* (2005) (LLS: 30 steps)

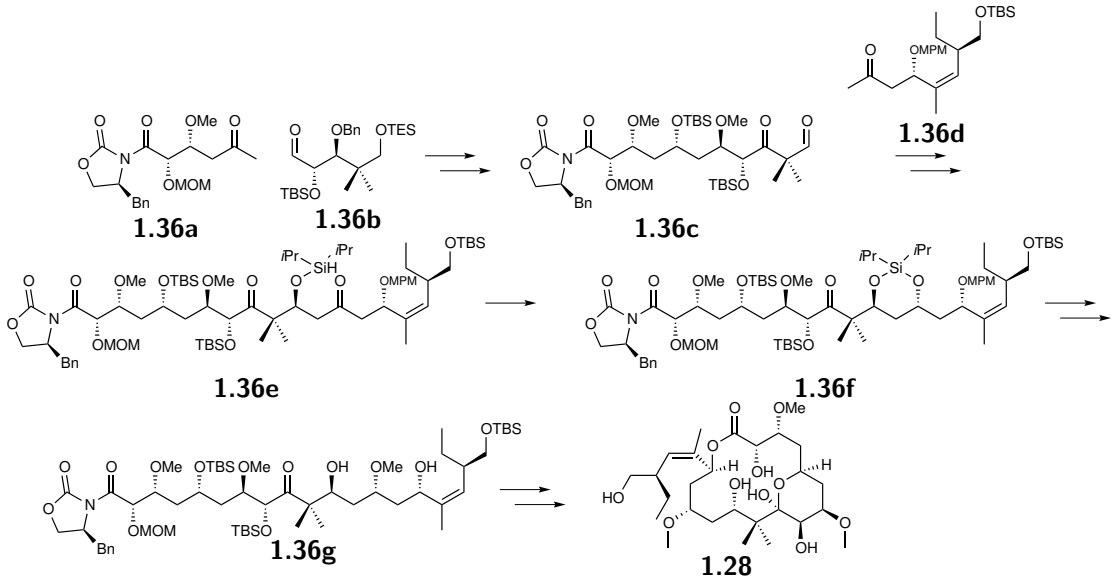
In the total synthesis of Ghosh *et al.*[56] (2008) chain elongations of **1.35a** are achieved using Brown's allylation and Horner-Wadsworth-Emmons olefination to form **1.35b** (scheme 1.4). This is further transformed to aldehyde **1.35c** by em-



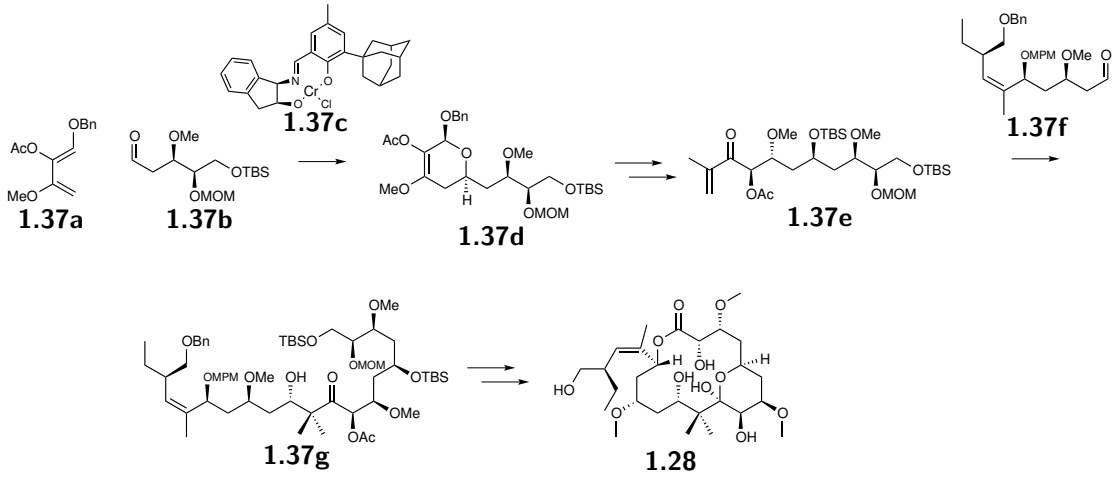
Scheme 1.4: Synthesis of (+)-peloruside A by Ghosh *et al.* (2008) (LLS: 29 steps)

ploying Sharpless's asymmetric dihydroxylation. Grignard attack and oxidation deliver enone **1.35d**. A novel reductive enolization followed by a stereoselective aldol reaction with aldehyde **1.35e** results in **1.35f**. After macrolactonization to **1.35g** (64% yield), the pyranose ring of peloruside **1.28** is formed in the final deprotection step.

The group of Evans published a total syntheses of peloruside in 2009 (scheme 1.5).[57] Methyl ketone **1.36a**, itself obtained by chiral auxiliary-mediated aldol chemistry, was coupled with aldehyde **1.36b**. After the necessary transformations, keto-aldehyde **1.36c** was formed. The hydroxyketone, resulting from the coupling between **1.36c** and methyl ketone **1.36d** was converted to silane **1.36e**. At this point, the stage was set for one of the key steps of this synthesis: the highly selective tin-mediated intramolecular silane reduction, to deliver **1.36f**. Further deprotection and selective methylation resulted in **1.36g**, which could be transformed to the natural product **1.28** in a straightforward fashion, *via* macrolactonisation (68% yield).



Scheme 1.5: Synthesis of (+)-peloruside A by Evans *et al.* (2009) (LLS: 22 steps)

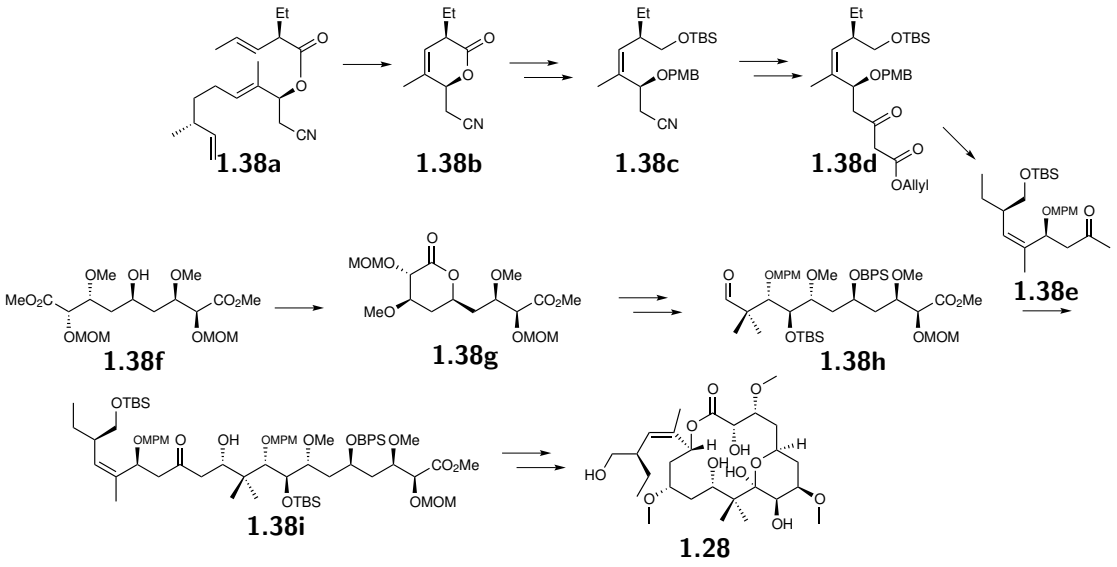


Scheme 1.6: Synthesis of (+)-peloruside A by Jacobsen *et al.* (2010) (LLS: 20 steps)

The year 2010 proved to be fruitful for the completion of total syntheses of peloruside: both the group of Jacobsen and Hoye published their work. The synthesis by Jacobsen[58] is characterized by highly selective catalytic reactions

involving epoxides for the synthesis of the building blocks. The most peculiar step in this synthesis, however, is a diastereoselective hetero-Diels-Alder reaction between diene **1.37a** and aldehyde **1.37b**, catalyzed by **1.37c** to build up a part of the pyranose precursor **1.37d** (scheme 1.6). This fragment is further transformed towards enone **1.37e**, which is coupled with aldehyde **1.37f** in a protocol which is similar to the one used in Ghosh's synthesis. The resulting hydroxyketone **1.37g** is conveniently transformed into peloruside **1.28**, again through macrolactonisation (52% yield).

The synthesis of Hoye is somewhat less elegant, as it requires more steps than any other peloruside synthesis. However, some ingenious strategies and technologies that were developed in his lab are implemented.[59]



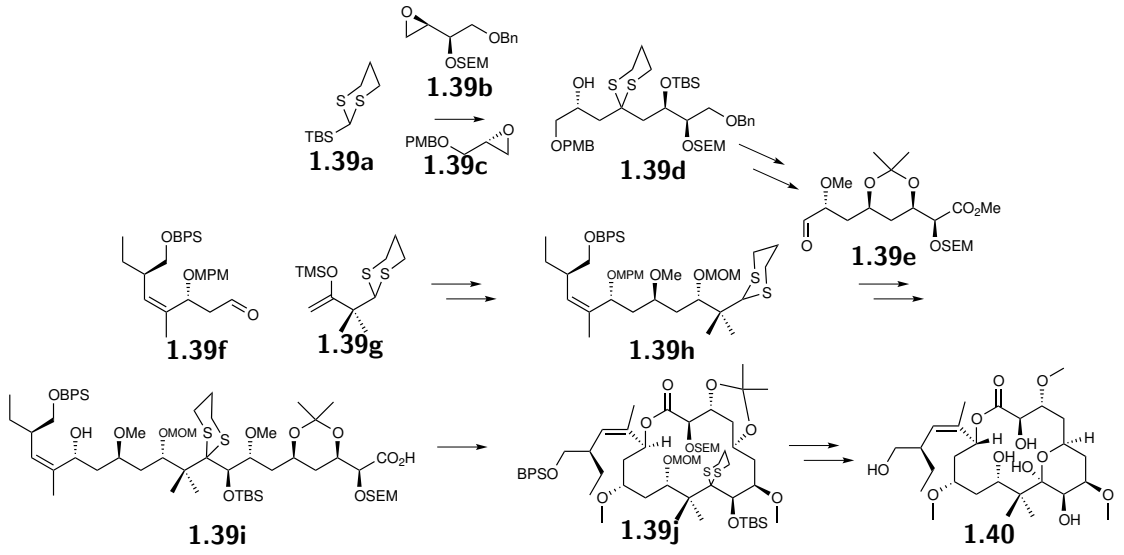
Scheme 1.7: Synthesis of (+)-peloruside A by Hoye *et al.* (2010) (LLS: 36 steps)

To install the trisubstituted olefin, precursor **1.38a** is transformed to lactone **1.38b** in a relay ring closing metathesis (scheme 1.7).[60] This is further elaborated towards **1.38c**, which undergoes a Blaise reaction and subsequent hydrolysis to form **1.38d**. A decarboxylation under neutral conditions provides methylketone **1.38e**. Another strategy that is implemented is the kinetic lactonization of

pseudosymmetrical **1.38f** to form **1.38g**.[61] This is further transformed to form aldehyde **1.38h**, which is coupled with methyl ketone **1.38e**, resulting in hydroxyketone **1.38i**. The macrolactone was formed with a yield of 54%.

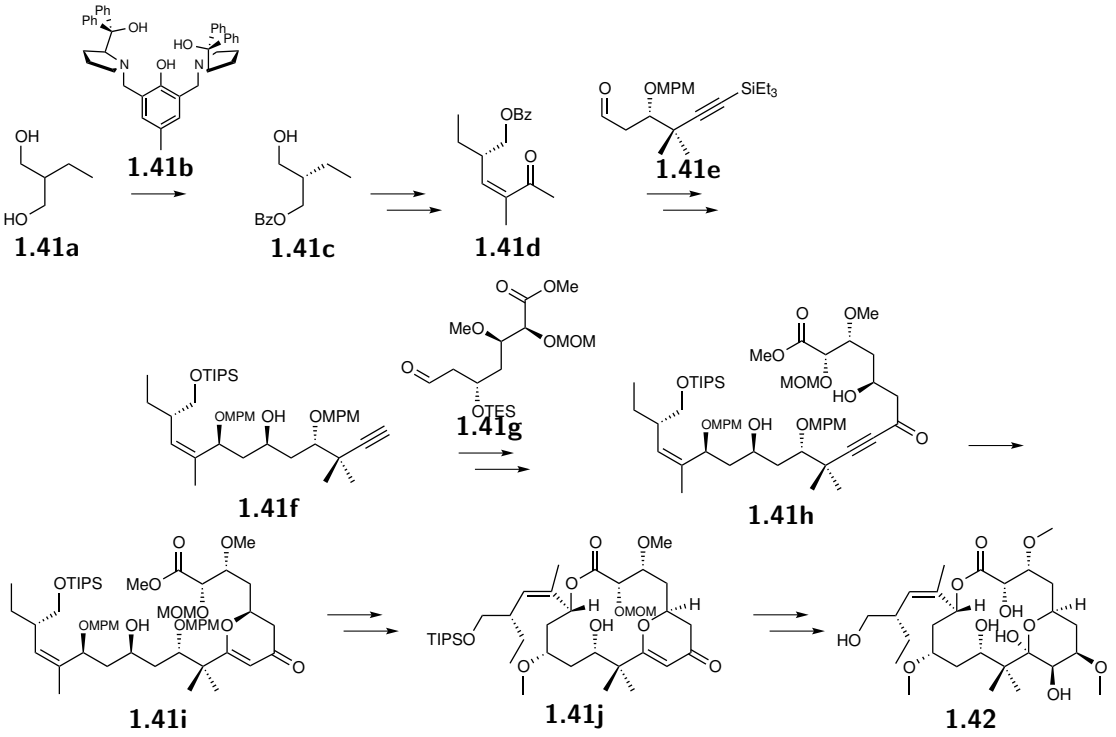
Total synthesis efforts of Smith III *et al.* and Trost *et al.*, resulted in the synthesis of epimers of peloruside.

The synthesis by the group of Smith III[62] was used to showcase the synthetic utility of type I anion relay chemistry.[63] The reaction product of the lithium anion of dithiane **1.39a** with epoxide **1.39b** undergoes Brook rearrangement and then attacks epoxide **1.39c** to form dithiane **1.39d** in one pot (scheme 1.8). This is further converted to aldehyde **1.39e**. On the other hand, aldehyde **1.39f** is reacted with silyl enol ether **1.39g** in a Mukaiyama aldol reaction. The fragment is then further transformed to dithiane **1.39h**, of which the anion reacts with the previously synthesis aldehyde **1.39e**. The coupled fragment is further converted to *seco* acid **1.39i**. During the macrolactonization of this fragment though, under Yamaguchi conditions at 90°C (70% yield), the stereocenter at C_2 was inverted, which went unnoticed until final deprotection, resulting in (-)-2-*epi*-peloruside **1.40**.



Scheme 1.8: Synthesis of (-)-2-*epi*-peloruside by Smith III *et al.* (2008) (LLS: 27 steps)

In the synthesis by Trost, desymmetrization of diol **1.41a** is achieved by employing catalyst **1.41b**, resulting in alcohol **1.41c** (scheme 1.9).[64] This was further converted to methyl ketone **1.41d** which is coupled in an aldol reaction with aldehyde **1.41e**. The anion of alkyne **1.41f** reacts with advanced aldehyde **1.41g**, to deliver ynone **1.41h** after oxidation. A gold-catalyzed cyclization delivers dihydropyranone **1.41i**. Trost employs thus an alkyne as a linchpin for assembling the carbon framework of peloruside, and takes advantage of the reactivity of this triple bond to construct the pyranose ring. Macrolactonization towards **1.41j** (57% yield) and subsequent conversion of the dihydropyranone to the pyranose ring are necessary to complete the synthesis. In the end, it was observed that the wrong (enantiomeric) catalyst in the synthesis of the side chain was used, resulting in the C_{18}-epimer **1.42**.



Scheme 1.9: Synthesis of (-)-18-*epi*-peloruside by Trost *et al.* (2013) (LLS: 22 steps)

1.2.3 Biological activity

Peloruside exerts its biological activity through binding to microtubuli. A focus on some physiological and pathological concepts is thus necessary to discuss this.[65–72]

The structure, dynamics and function of microtubuli

Microtubuli are key components of the cytoskeleton, consisting of highly dynamic fibres. These cylindrical fibres are formed by the association of heterodimers consisting of alpha- and beta-tubulin, which are tightly bound together (figure 1.13a). Each type of tubulin subunit has a binding site for GTP: a non-hydrolyzable site on alpha-tubulin and a hydrolyzable site on beta-tubulin. They assemble in a head-to-tail arrangement, leading to linear protofilaments with a distinct structural polarity. Sets of thirteen protofilaments are kept together by forming lateral contacts, and further polymerize, resulting in the hollow microtubule cylinder with beta-tubulin exposed at the so-called (+)-end and alpha-tubulin at the so-called (-)-end.

The annotation '(+)-end' emanates from the fact that the highly dynamic behaviour of microtubules (growing as well as shrinking) manifests itself mainly at this end. In order to polymerize, microtubules use energy provided by the hydrolysis of GTP. Thus, the free beta-tubulin subunit must be bound to GTP at its hydrolysable site before assembly into microtubules can occur. Shortly after the addition, GTP is irreversibly hydrolyzed to GDP. The majority of beta-tubulin in the microtubule is thus in the GDP-bound state and capped with GTP-bound tubuline at its (+)-end. It is generally considered that, upon hydrolysis, the conformation of GTP-bound tubulin changes from a straight to a more curved form, inducing conformational strain.

When the GTP on a beta-tubulin is hydrolyzed to GDP before another GTP-bound beta-tubulin is added (loss of the protective GTP-cap), the conformational change of the exposed GDP-bound beta-tubulin results in rapid depolymerization, known as a 'catastrophe' (figure 1.13b). When the addition of free tubulin-dimers

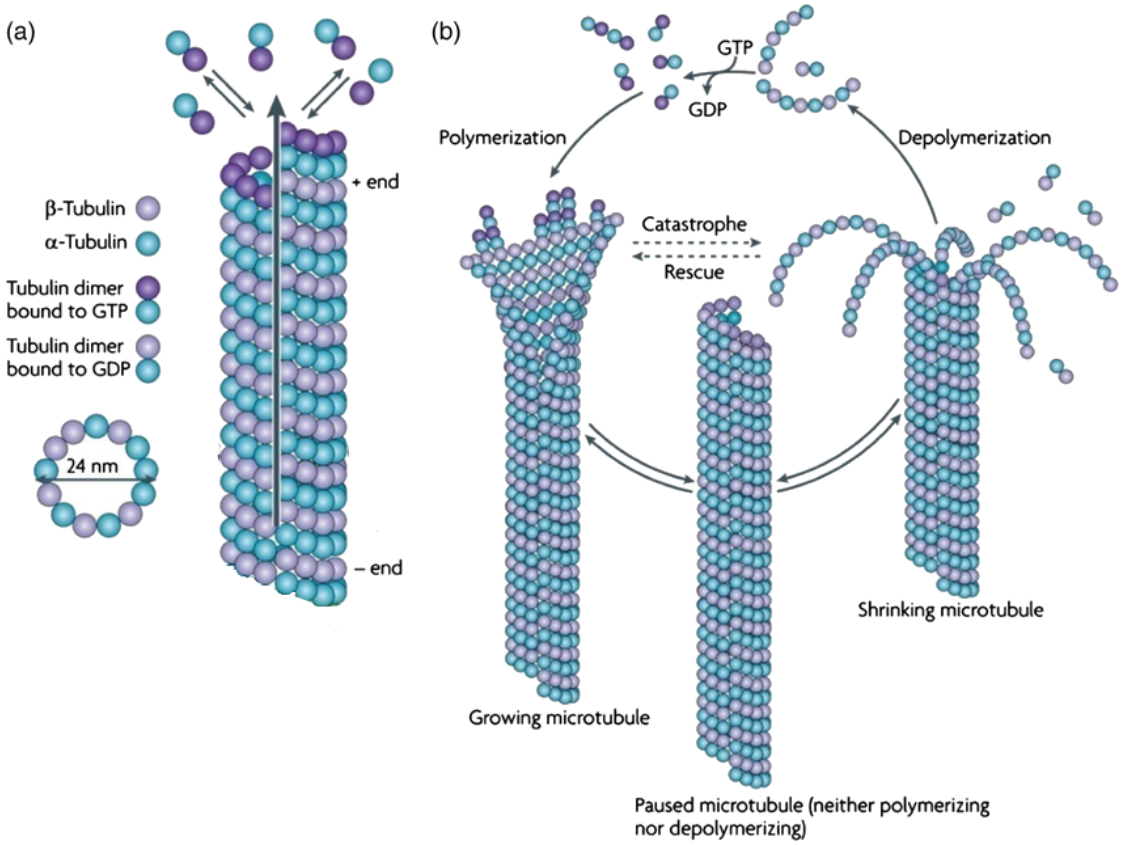


Figure 1.13: Schematic representation of the dynamics of a microtubule. Reprinted by permission from Macmillan Publishers Ltd:[73] Copyright 2009.

at the GTP-cap is faster than hydrolysis to GDP, the microtubule is growing, also known as a 'rescue'. The process in which the individual microtubule ends switch between phases of growth and shrinkage is called dynamic instability. In contrast, a more subtle dynamic behaviour, consisting of net growth at one microtubule end and balanced net shortening at the opposite end is called 'treadmilling'. It is the combination of these dynamic phenomena that determines and regulates the biological functions of microtubules in all cells.

The highly organized arrangement and the dynamics of microtubules are crucial in maintaining the cell shape, in the transport of different cell components, in cell signalling and in cell division and mitosis in particular.

Microtubules as target for the treatment of cancer

The eukaryotic cell cycle is tightly controlled by a number of cyclin dependent protein kinase complexes (CDK complexes), through a series of phosporylation/ dephosphorylation events. Cells transverse the cell-cycle in two main phases: interphase, consisting out of the G1, S and G2 phase, and mitosis. These processes are depicted in figure 1.14.

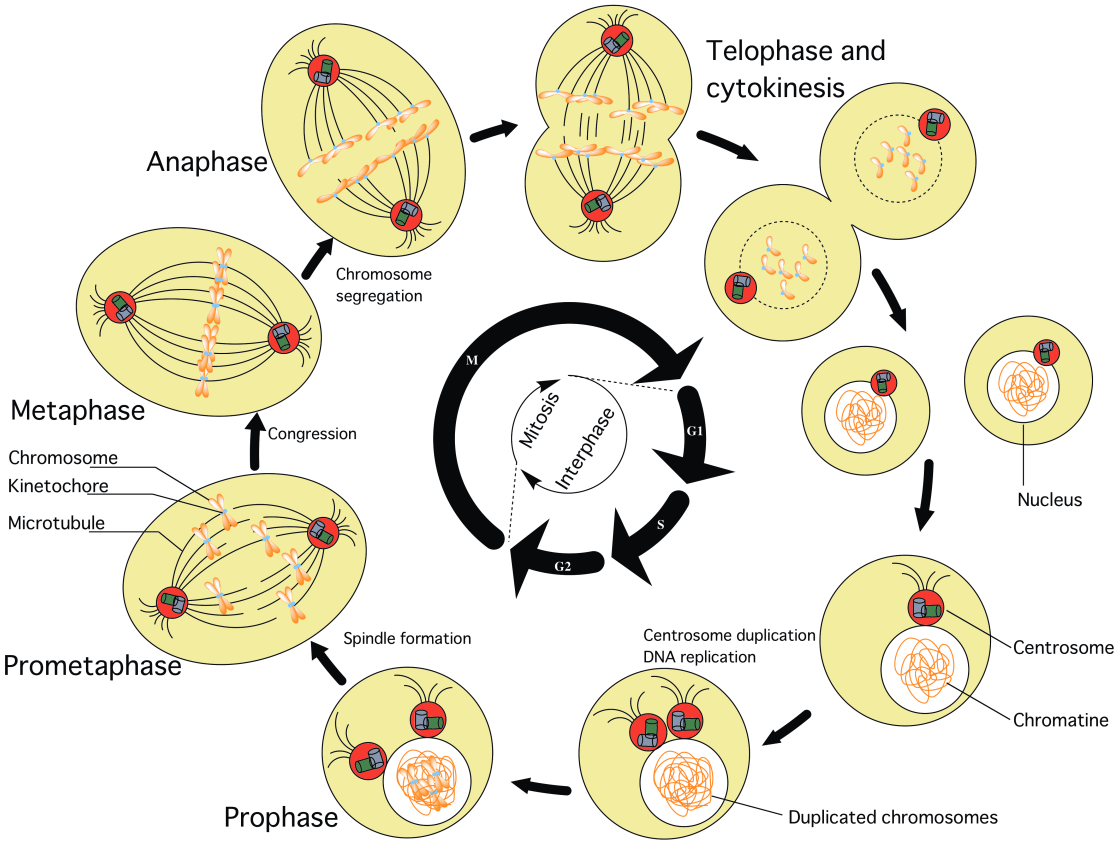


Figure 1.14: Schematic representation of the cell cycle. Adapted by permission from Macmillan Publishers Ltd:[74] Copyright 2014.

In the G1 phase, cells commit to enter the cell cycle and prepare to replicate their DNA and duplicate their centrosomes.

The actual replication and duplication occurs in the S phase. S phase CDK

complexes phosphorylate prereplication complexes, inducing one round of replication initiation. Each chromosome is replicated, forming two sister chromatids, connected by cohesin molecules. Mitotic CDK complexes are made during S phase en G2, but their activities are inhibited until correct DNA synthesis is complete. Any defect in DNA replication might be repaired during G2 phase. Activation of mitotic CDK complexes causes initiation of mitosis.

At the onset of mitosis the chromosomes and centrosomes of the cell have been replicated. During early prophase, the chromosomes condense. Later in prophase, the centrosomes begin to move toward opposite poles. At each centrosome, microtubules are nucleated and elongate. At prometaphase, the nuclear envelope breaks down and microtubules attach to the kinetochores, specialized sites at each chromosome centromer. This is achieved by a stochastic process in which kinetochores of the chromosomes are captured by randomly elongating and contracting microtubules emanating from the two spindle poles. Eventually, sister centromers are attached to the microtubules from opposite poles. During metaphase, kinetochore microtubules guide the alignment of sister chromatids at the equatorial plane of the cell, a process called 'congression'.

Next, the anaphase promoting complex (APC) is activated. APC targets cohesin regulators for degradation, allowing segregation of sister chromatids. During anaphase, sister chromatids are separated as the kinetochore connected microtubules pull them toward opposite poles. Subsequently, APC also degrades mitotic CDK complexes, resulting in the final mitotic events: the cell elongates and cytokinesis (ring contraction) begins. In telophase, a nuclear membrane reforms around each daughter nucleus and the chromosomes decondense. Mitosis results in two identical daughter cells, each are containing two copies of every chromosome.

Cell cycle progression is monitored by checkpoint mechanisms that ensure faithful duplication, and accurate chromosome segregation and distribution during mitosis. The mitotic spindle assembly checkpoint monitors that all chromosomes have achieved bivalent attachment to microtubules and that a tension is generated through microtubule-mediated pulling of kinetochores to opposite directions.

It is clear that well controlled dynamics of microtubules are indispensable for correct cell division: for the reorganization of the existing network during the transition from interphase to mitosis, and at different stages during mitosis. Any disruption of the microtubule dynamics will lead to cell-cycle arrest and will eventually result in cell death.

As many cancer cells divide more frequently than normal cells, they pass through mitosis more often and they become particularly susceptible to agents that disrupt the microtubule dynamics. These agents are therefore called microtubule inhibitors, antimitotic drugs or spindle poisons and belong to the most used treatments of cancer.

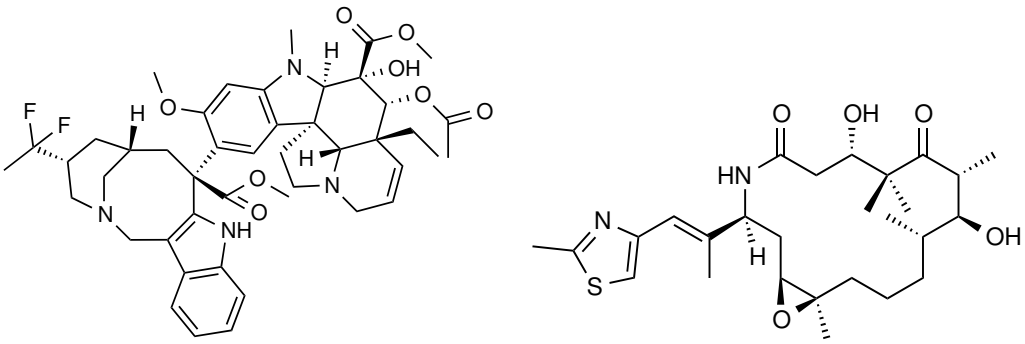
The microtubule inhibitors are usually classified in two main groups. One group, the *microtubule-destabilizing agents*, inhibits microtubule polymerization at high concentrations. An example of this is vinflunine (Javlor®) (**1.43**, figure 1.15), which is in clinical use for the treatment of different types of cancer.

The second group are the *microtubule-stabilizing agents*. These agents promote microtubule polymerization at high concentrations. Paclitaxel (Taxol®) was the first agent to be identified in this class. Other examples include docetaxel (Taxotere®) and ixabepilone (Ixempra®) (**1.44**), which are also commonly used in the clinic. Also (+)-peloruside A, the subject of this dissertation, is classified as a microtubule-stabilizing agent.[i] Peloruside was reported to show cytotoxic activity at nanomolar concentrations in different cancer cell lines.[75,76]

Microtubules as target for the treatment of neurodegenerative diseases[77–79]

Another therapeutic area where microtubule stabilizing agents can be employed, is the area of neurodegenerative diseases.

[i] The classification of anti-cancer drugs as microtubule 'stabilizers' or 'destabilizers' is actually simplistic. Polymerization, and inhibition of polymerization respectively, have only an effect on the mass of the microtubule-polymer at high concentrations. At clinically relevant concentrations, the effect of the drugs in suppressing the microtubule dynamics is far more powerful than the effects on polymer mass.[67]



1.43 **1.44**

Figure 1.15: Vinflunine (**1.43**) and Ixabepilone (**1.44**)

Neurons are nerve cells that transmit nerve signals to and from the brain. The neuron consists of a cell body with branching dendrites, and a projection, called axon, which conducts the nerve signal (figure 1.16). At the other end of the axon, the axon terminal transmits the electro-chemical signal across a synapse. This is the gap between the axon terminal and the receiving cell.

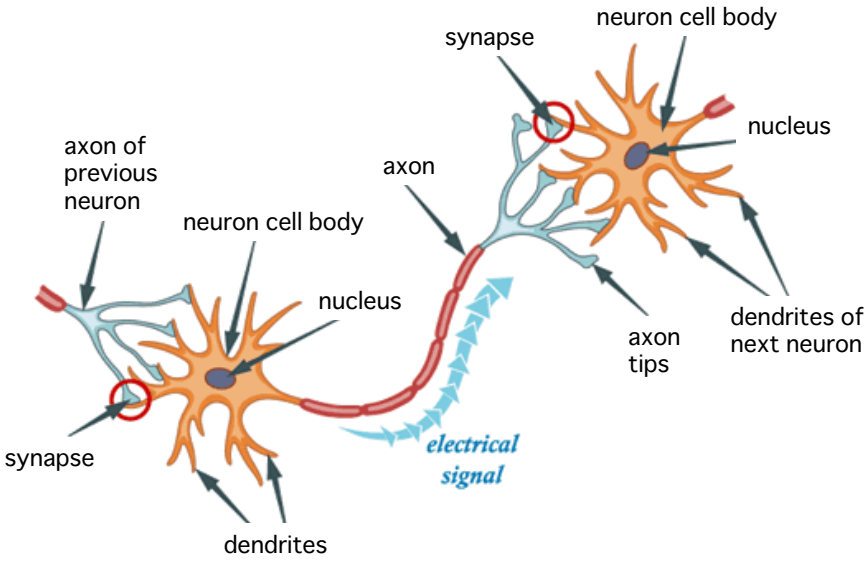


Figure 1.16: The structure of a neuron[80]

In the axons of neurons, microtubules form polarized linear arrays with the

plus ends directed toward the synapses and the minus ends toward the cell body. In this way, the microtubules provide both structural support and directionality for the intracellular transport of proteins and vesicles between cell body and synapse. This cytoskeletal structure, together with molecular motor proteins such as kinesins and actins, comprise the axonal transport machinery. This machinery is critical for the viability of a neural cell, and defects in axonal transport are observed in several neurodegenerative diseases. Particularly in the axons of neurons, microtubules are stabilized by the microtubule associated protein *tau*. When *tau* is hyperphosphorylated, the binding affinity of this protein for microtubules is reduced, and it becomes disengaged. An abnormal detachment of *tau* from the microtubules, alters the dynamics and organization of the axonal microtubules, which causes axonal transport defects. Furthermore, free and hyperphosphorylated *tau* is more prone to misfolding and aggregation, which can recruit functional *tau* into an aggregation cascade, and thereby worsening the destabilization of axonal microtubules.

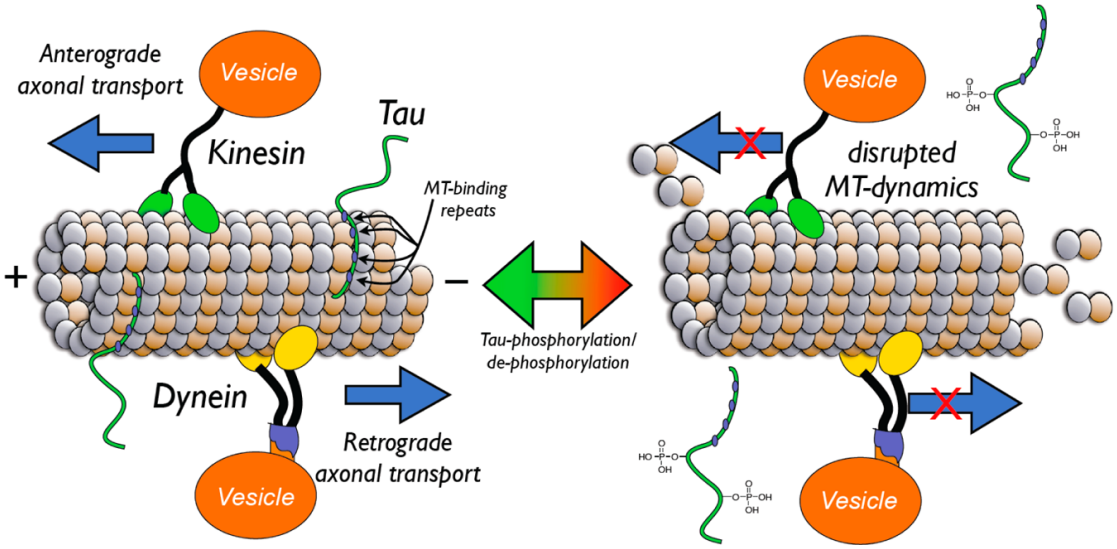
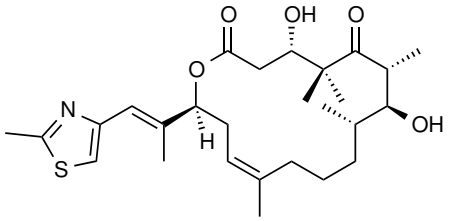


Figure 1.17: Axonal transport defects caused by *tau* phosphorylation. Reprinted with permission from[79] Copyright 2012 American Chemical Society

By employing exogenous microtubule-stabilizing agents, the loss of *tau* could be

compensated, thereby maintaining the appropriate organization and dynamics of the microtubuli. The MSA epothilone D (**1.45**) proved to be efficient in doing this, both *in vitro* and *in vivo*, and moved on to phase I clinical trials. Unfortunately, it was discontinued due to side effects.



1.45

Figure 1.18: Epothilone D

In an *in vitro* assay, peloruside is effective in protecting the neurons against phosphorylation of tau, however, it remains unclear whether it will penetrate the blood-brain-barrier, which is of utmost importance in the treatment of CNS diseases.[78]

The potential of (+)-Peloruside A as treatment for cancer, neurodegenerative diseases or even autoimmune diseases has been recently reviewed by Miller *et al.*.[81]

Binding pocket of (+)-peloruside A

In 2004, the group of Miller investigated the cytotoxicity of peloruside in paclitaxel-resistant cell lines.[82] This resistance can be a result of overactivation of active transport mechanisms, like the permeability glycoprotein (Pgp), or because of mutations of the β-tubuline gene, which encodes for the binding pocket of paclitaxel (taxoid binding site). It was observed that peloruside retains its activity in these resistant cell lines, suggesting it binds to a distinct location. Also the microtubule-stabilizing agent laulimalide retained its activity, which meant both peloruside and laulimalide bind to the same (or at least overlapping) binding pocket.

Further experiments showed that peloruside shows synergism with other (taxoid binding) MSA's. No evidence of synergism between laulimalide and peloruside

was observed, which supports the earlier stated hypothesis of a common binding pocket between these. Furthermore, this was supported by peloruside being replaced by laulimalide, but not by other (taxoid binding) agents.

There has been a lot of discussion on the exact binding pocket of peloruside on tubuline, and a lot of research has been done by different groups. Initial molecular modelling experiments by Vilarrasa in 2004 suggested a pocket on α-tubulin.[83] Jiménez-Barbero and Díaz also suggested a binding pocket on α-tubulin, based on advanced NMR studies and molecular mechanics calculations.[84] The same study also provided the bioactive conformation of peloruside, both in the free state and bound to tubulin.

Another study combined advanced MS experiments, using the exchange of hydrogen and deuterium to map the binding interactions (HDX-MS), together with computational simulations and came up with a binding pocket on β-tubulin.[85]

Both above suggestions were, as it seems, combined in a new proposal, by the groups of Barasoain and Díaz.[86] This suggestion comprised the binding of peloruside in a two-step mechanism (as is the case for paclitxel), of which the initial event is the binding to β-tubulin, upon which the ligand is transported to the inside of the α-tubulin. The same research indicated that the primary free alcohol at C_{24} is essential for binding.

Hamel *et al.* used the docking site of Huzil (originating from the HDX-MS experiments), but reoriented peloruside in this site, thereby enabling the introduction of new hydrogen bonds and hydrophobic interactions.[87] This resulted in an updated binding interactions profile between peloruside and β-tubulin (figure 1.19)

In 2011, the isolation of a series of peloruside-resistant cell lines was achieved. From experiments on these cell lines, in combination with HDX-MS, it was shown that the mutations result in a conformational change in a cleft where the side chain is predicted to dock. This illustrates the importance of the side chain in the binding process.[88]

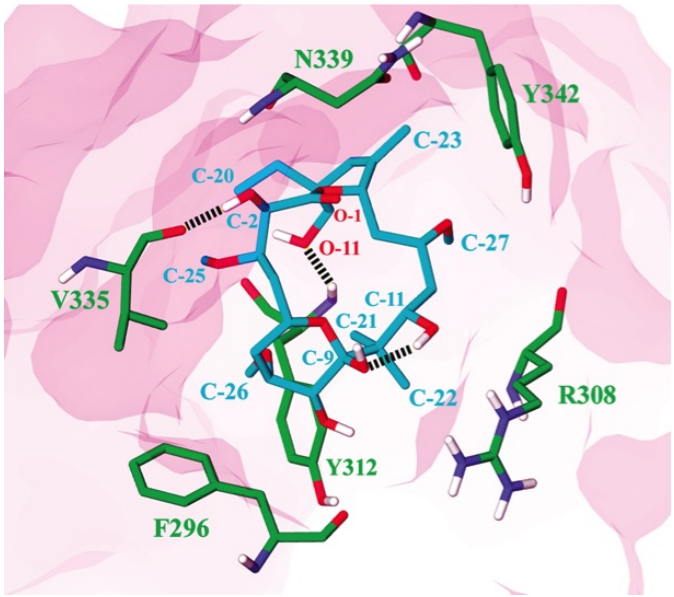


Figure 1.19: Important binding interactions between (+)- peloruside A and β-tubulin, according to Hamel *et al.* Reprinted with permission from[87] Copyright 2010 American Chemical Society.

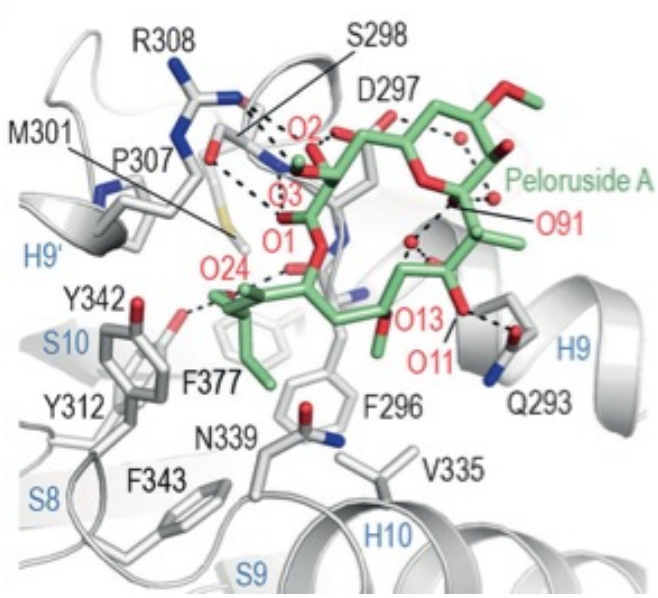


Figure 1.20: Important binding interactions between (+)- peloruside A and β-tubulin, identified by means of X-ray crystallography. Reprinted by permission of John Wiley and sons from[89] Copyright 2014.

Proof of the actual binding site of peloruside was delivered in 2014 by Steinmetz's group by means of X-ray crystallography.[89] They were able to determine the tubulin-bound peloruside structure and suggested that peloruside is able to bridge two adjacent tubulin dimers. Together with the important binding interactions (figure 1.20), they came up with a rationale for the observed synergistic interactions between peloruside and e.g. paclitaxel: by means of an allosteric interaction, induced by peloruside, the binding pocket of the taxanes becomes stabilized.

Analogs of (+)-peloruside A and their activity

Besides (+)-peloruside A, three other natural congeners of peloruside exist, peloruside B (**1.46**), C (**1.47**) and D (**1.48**) (figure 1.21).[90,91] Peloruside B only differs from A by the absence of an O-methyl group linked to the C_3 alcohol, and has a similar biological activity. In the case of peloruside C, which differs in degree of

oxidation at the pyran, the cytotoxicity is reduced, but still present. In the case of Peloruside D on the other hand, where the pyran ring has shifted, cytotoxicity is only observed at far higher concentrations (millimolar range).

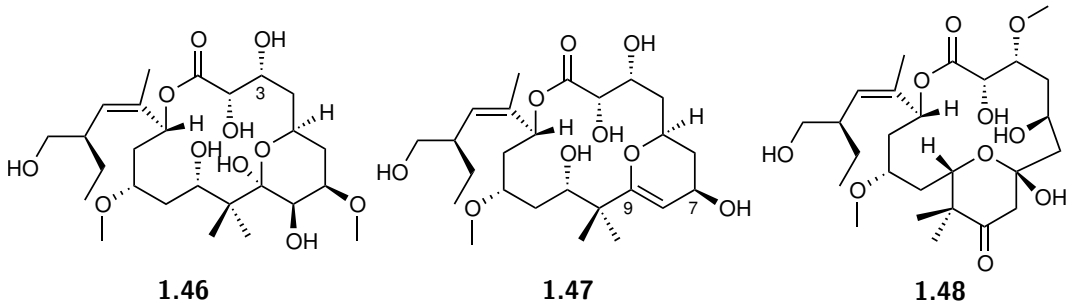


Figure 1.21: Natural occuring congeners of (+)-peloruside A

Besides the earlier described C_2- and C_{18}-epimers, of which no biological data are available, also the C_{11}-epimer (**1.49**) was described in a patent by Ghosh (figure 1.22).[92] Intriguingly, this epimer had a comparable bioactivity as the original peloruside A. In this same patent, Ghosh also described the experimental and biological data for 2 analogs lacking the oxygen at C_2: one with the original methoxy at C_7 (**1.50**) and one with the free alcohol at this position (**1.51**). A drop in activity was observed, suggesting the alcohol at C_2 is important for binding.

A bunch of deoxygenated analogs were synthesized. Both *E* and *Z* $C_{12}-C_{13}$ unsatured analogs (**1.52** and **1.53**) were synthesized by Zhao and Taylor,[93] lacking oxygens at C_{11} and C_{13} (figure 1.22). The rationale behind this was the prediction of NMR and computational studies that the C_9-C_{15} region of the original natural product is flexible compared to the rigid C_2-C_3 and C_5-C_9 region. Unfortunately, the analogs were too unstable to perform biological experiments.

The group of Altmann synthesized a THP analog (**1.54**), lacking the substituents at C_7, C_8 and C_9,[94] and two monocyclic analogs (**1.55** and **1.56**), where the embedded ring is missing (figure 1.23).[95,96] Of the latter two, one (the *R*-analog, **1.55**) has a hydroxyl in an equivalent position as the hemiacetal group in peloruside A. The activity of the THP analog **1.54** is only 10 fold lower, compared

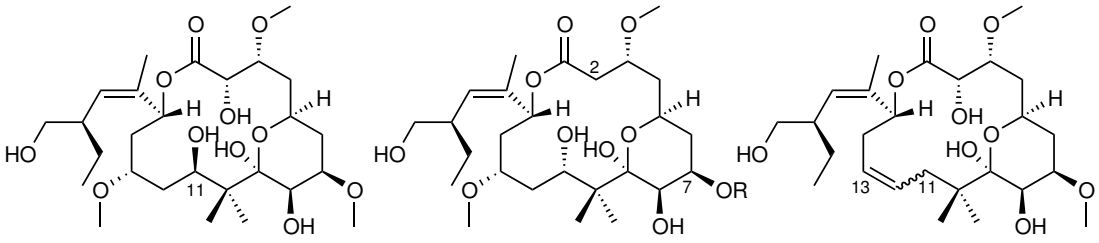


Figure 1.22: Synthetic analogs of peloruside (1)

to the natural product. For the (7*S*) monocyclic analog, the biological activity was non existing, whereas the (7*R*) analog still showed a modest activity in the micromolar range. The strongly simplified analog **1.57** did only show very modest activity.[97]

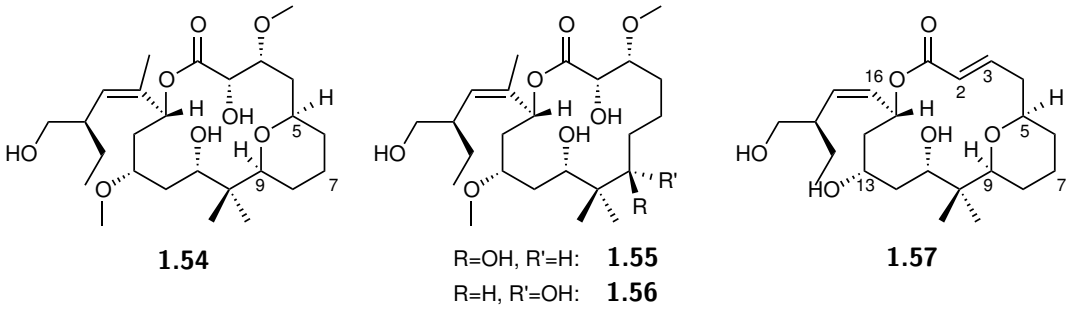


Figure 1.23: Synthetic analogs of peloruside (2)

The $NaBH_4$ reduction product of natural peloruside (**1.58**)[75] and the 2-deoxy analog (**1.59**)[92] were also reported (figure 1.24). The former showed a ten-fold decrease in activity, whereas the latter was completely inactive.

The importance of the free alcohol at C_{24} was shown by derivatizing natural peloruside. Upon acetylation of the primary alcohol (**1.60**), the activity was ten times lower, whereas chloroacetylation of the primary alcohol resulted in an analog (**1.61**) with comparable activity as the natural product.[86] This is probably due to hydrolysis of the ester *in vitro*, resulting in the *in situ* formation of peloruside A.

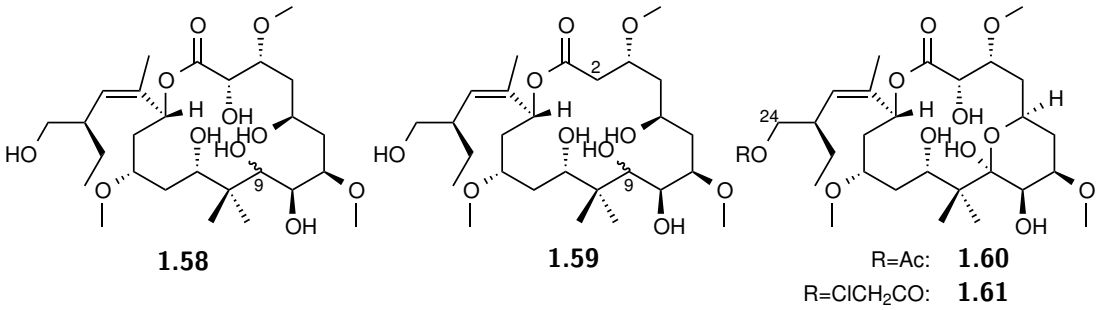


Figure 1.24: (Semi)-synthetic analogs of peloruside (3)

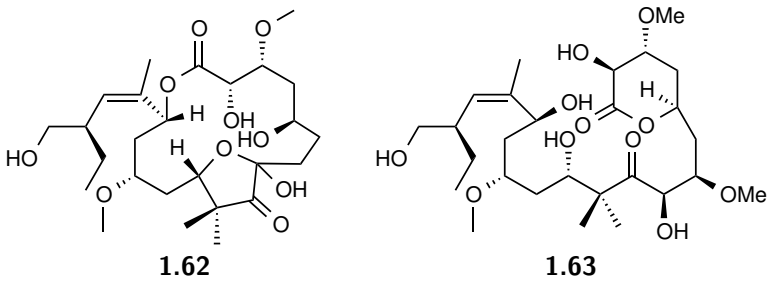


Figure 1.25: Semi-synthetic analogs of peloruside (4)

The treatment of natural peloruside with acid delivered different analogs, depending on the acid (figure 1.25). When catalytic TFA was employed, a furanose analog (**1.62**) was formed, whereas, upon the use of trifluoromethanesulfonic acid, a pyranone analog was obtained (**1.63**).[91] The activity of these analogs is in the micromolar range.

All the aforementioned analogs are discussed in detail in a recently published review[98] and their activity is summarized in table 1.1.

Compound	HL-60	P388	A2780	HCT116
1.28	7-35	18	19	
1.46	33			
1.47	221			
1.48	2000			
1.49		10		
1.50		120		
1.51		320		
1.54				163
1.55				1170
1.56				>20000
1.57				15000
1.58	221			
1.59		>5000		
1.60			257	
1.61			27	
1.62	15000			
1.63	7000			

Table 1.1: IC_{50}-values of peloruside analogs in specified cell lines (nM) (HL-60: human leukaemia cells, P388: murine leukaemia cells, A2780: ovarian carcinoma cells, HCT116: colon carcinoma cells).

2

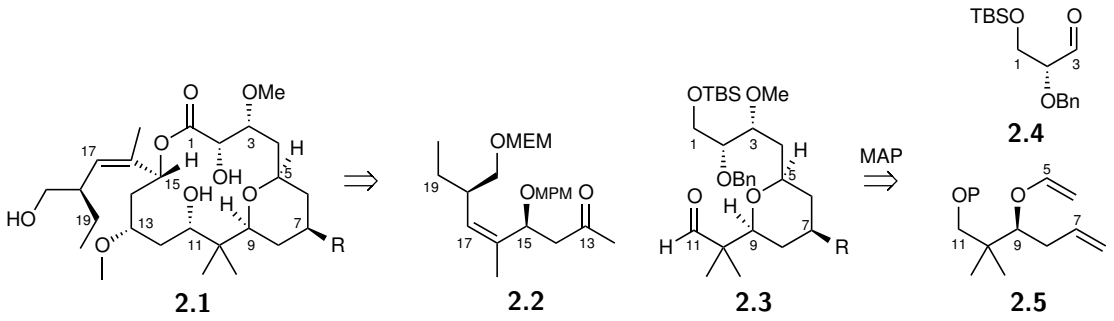
Tetrahydropyran analogs

In this chapter, the synthesis towards a first set of analogs is described. The main challenge was the implementation of a fairly unexplored reaction to introduce chemical complexity, while opening up possibilities for diversification, and analog development.

2.1 Introduction

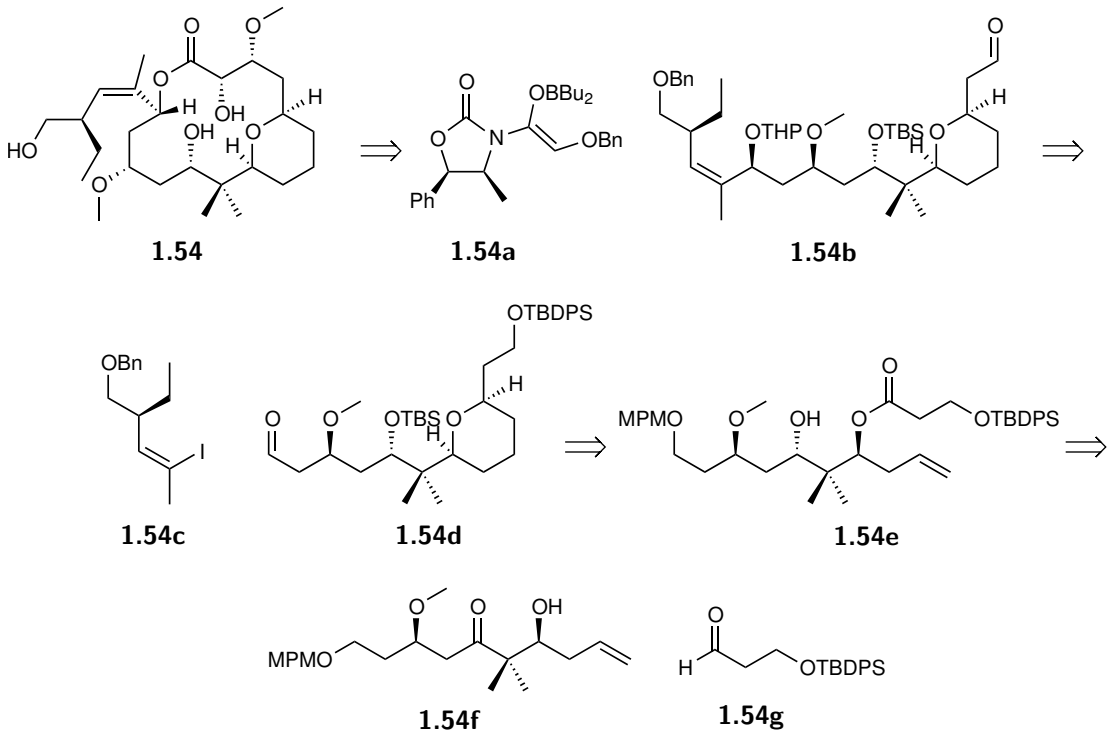
In order to investigate the importance of the hemi-acetal function in peloruside and the substituents on the pyranose ring, a set of analogs was designed where this pyranose ring is replaced by a tetrahydropyran (THP) ring, whether or not with a substituent at the C_7 position (**2.1**).

Our design is based on the aldol coupling of two advanced intermediates: a methyl ketone **2.2**, containing two stereocenters and the trisubstituted double bond of the side chain, and an aldehyde **2.3**, containing the (substituted) THP ring and two additional stereocenters (Scheme 2.1). The synthesis of the latter fragment was based on the Mukaiyama-aldol Prins (MAP) cyclization,[99] a cascade/domino reaction between an aldehyde **2.4** and a bisnucleophile **2.5**, in the presence of a Lewis acid.



Scheme 2.1: Retrosynthetic analysis of the envisaged THP analogs

During the course of this PhD, in 2013, the synthesis of the 7,8,9-trideoxy analog **1.54** (thus with an unsubstituted THP-ring) was published by the group of Altmann (scheme 2.2).[94] Key steps include glycolate aldol addition of boron-enolate **1.54a** to aldehyde **1.54b**, a vinyllithium addition of the corresponding lithiate of **1.54c** to **1.54d**. The THP ring of the latter compound is constructed from **1.54e** *via* a Prins cylization with $CeCl_3$ and LiI. Hydroxyester **1.54e** is the result of an Evans-Tishchenko reduction (*vide infra*) of hydroxyketone **1.54f** with aldehyde **1.54g**.

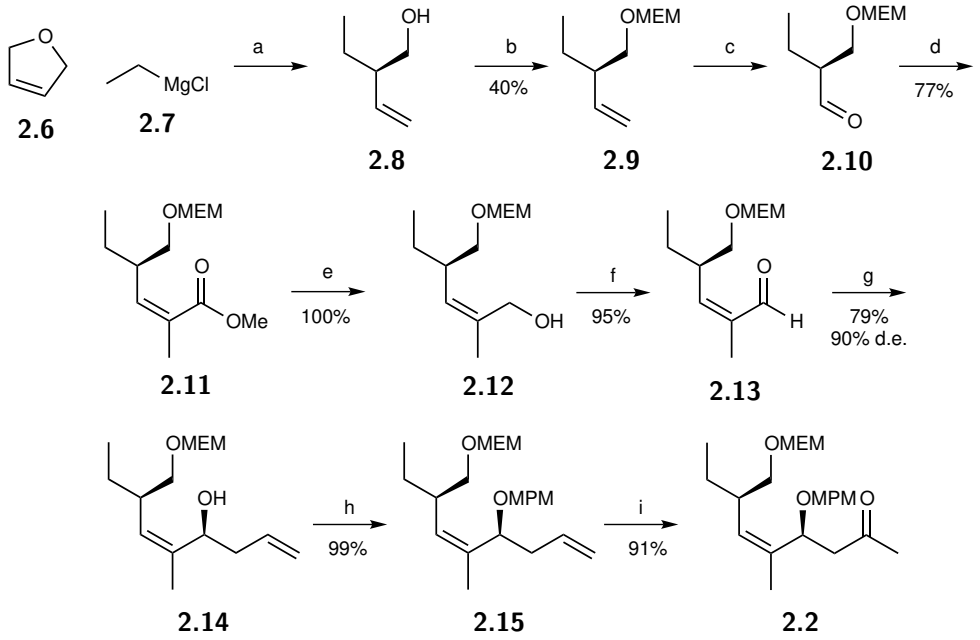


Scheme 2.2: Retrosynthetic analysis of the 7,8,9-trideoxy-analog **1.54** by Altmann

2.2 Synthesis of the C_{12}-C_{20} methyl ketone 2.2

The synthesis of the C_{12}-C_{20} fragment was developed earlier in our lab as part of a Master thesis and is represented in figure 2.3.[100] In literature, the installation of the stereocenter at C_{18} is usually accomplished using a chiral auxiliary, or making use of asymmetric transition metal catalysis. Here, the catalytic approach for the formation of **2.8** is preferred, as it is shorter and more elegant. Also, this procedure was reported in literature.[101,102] The zirconium-catalyzed asymmetric carbomagnesation was developed in the lab of Hoveyda and encompasses the enantioselective addition of a Grignard reagent to an 'activated' *Z*-alkene.

The chiral catalyst used is (*S,S*)-ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)zirconium (*R*)-1,1'-bi-2-naphtolate ((*S,S*)-(EBTHI)ZrBINOL) (**2.16**). The corresponding proposed catalytic cycle is depicted in scheme 2.4 and starts with



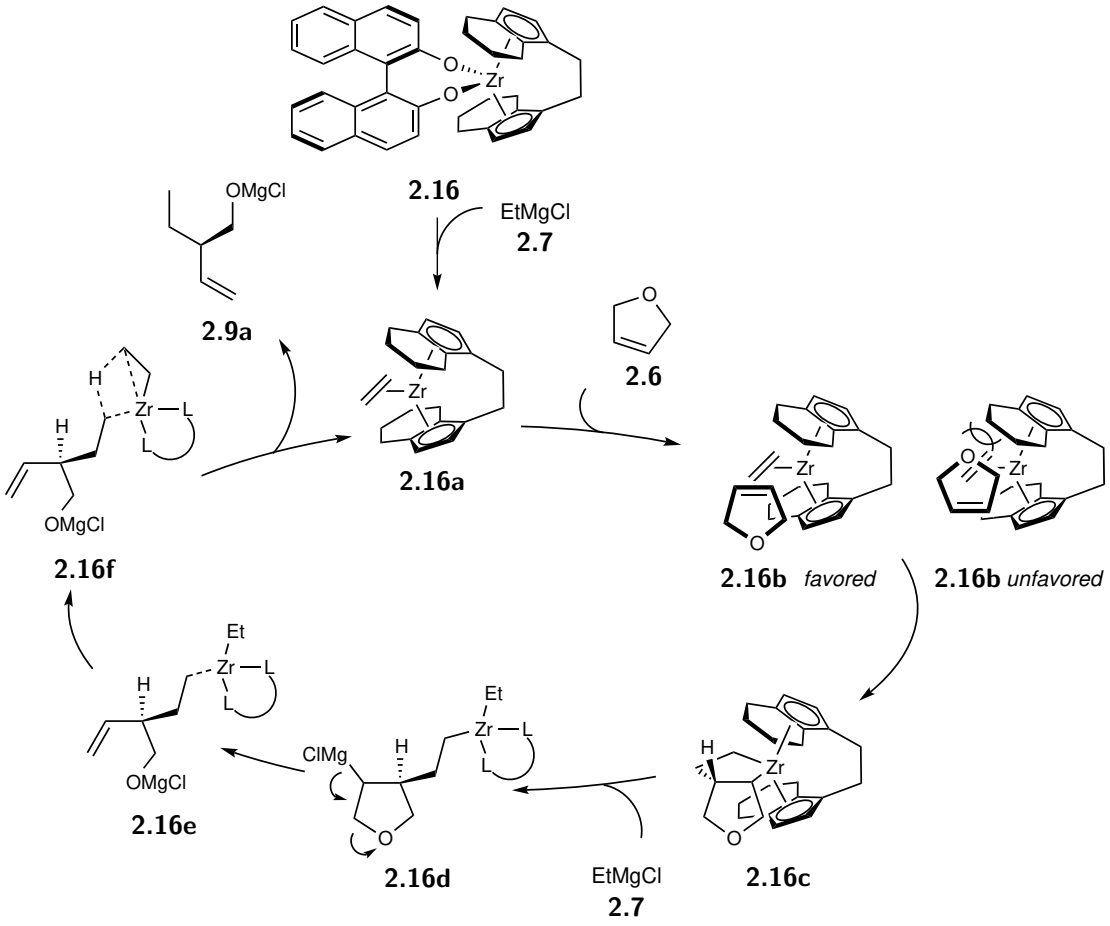
a) [(*S,S*)-ethylene-bis(4,5,6,7-tetrahydro-1-indenyl)]Zr(IV)BINOL **2.16** , THF, 40h, RT; b) DIPEA, MEM-Cl, CH_2Cl_2, reflux; c) [i] O_3, CH_2Cl_2, -78°C; [ii] Ph_3P, CH_2Cl_2; d) 18-crown-6, KHMDS, THF, -78°C, $(CF_3CH_2O)_2POCH(CH_3)CO_2CH_3$; e) DIBAL-H, CH_2Cl_2, -78°C, 1h; f) DMP, pyridine, CH_2Cl_2, 1h, rt; g) [i] (-)-Ipc$_2$BOMe, allylMgBr, Et_2O, -78°C; [ii] NaOH, H_2O_2, RT; h) [i] NaH, THF, 0°C; [ii] MPM-Cl, TBAI, DMF, RT; i) $PdCl_2$, $Cu(OAc)_2.H_2O$, DMF:H_2O 9:1, O_2, RT

Scheme 2.3: Synthesis of the C_{12}-C_{20} fragment (**2.2**)

the complexation of ethylene (**2.16a**) upon addition of EtMgCl to the catalyst. Next, enantioselective cycloinsertion of dihydrofuran (**2.6**), *via* **2.16b** leads to the formation of zirconacyclopentane intermediate **2.16c**.

The enantioselectivity of this insertion arises from the specific addition mode, avoiding any unfavorable interactions (**2.16b** *favored*), whereas approach *via* the alternative enantioface is blocked by the cyclohexyl unit of the tetrahydroindenyl ligand (**2.16b** *unfavored*). In this respect, the *cis*- geometry of the alkene, is very important to obtain high levels of stereoinduction. After insertion, upon attack of ethylmagnesiumchloride, the zirconacyclopentane **2.16c** is regioselectively cleaved, affording the less sterically hindered intermediate **2.16d**, which can irreversibly eliminate towards alkene **2.16e**. Subsequent β-hydride transfer from the ethyl (**2.16f**), followed by reductive elimination affords the magnesium alkoxide **2.9a**,

regenerating the catalytic species **2.16a**.

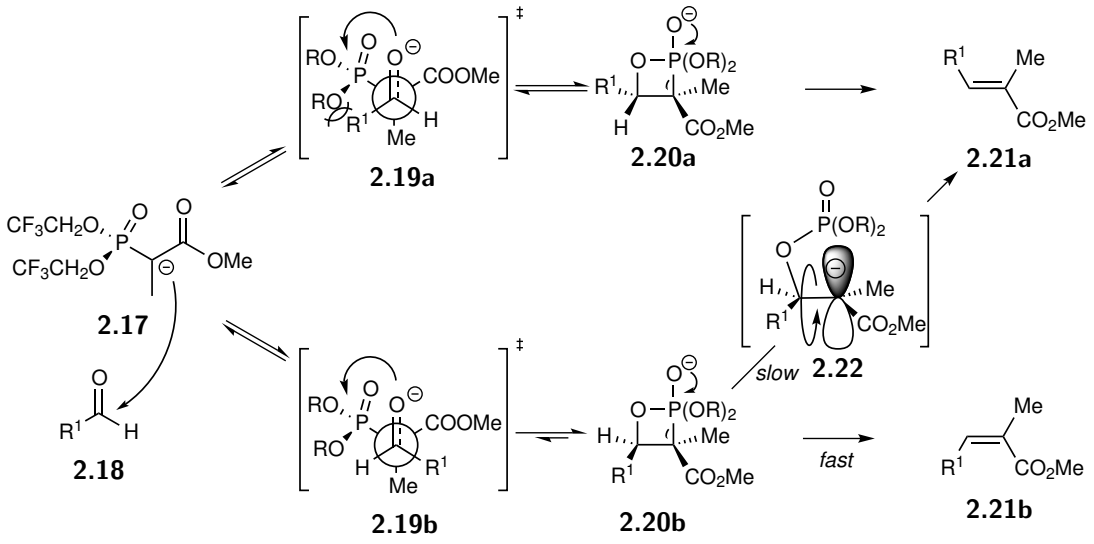


Scheme 2.4: Proposed catalytic cycle of the enantioselective zirconium-catalyzed carbomagnesation of **2.6**[101]

Homoallylic alcohol **2.8** was isolated after distillation at atmospheric pressure, at which stage the enantiomeric excess could be determined using chiral GC (enantiomeric ratio >98:2), which is in agreement with the values that are reported in literature.[101] The alcohol **2.8** was protected as MEM ether **2.9**, with a yield of 40% over two steps. This lower yield is explained as the amount of expensive catalyst is optimized in terms of turnover numbers more than in terms of absolute total yield.[103]

The resulting alkene **2.9** is then oxidatively cleaved using ozone (scheme 2.3),

and the resulting aldehyde **2.10** is subjected to the Still-Gennari variant of the Horner-Wadsworth-Emmons (HWE) olefination to form the α-β-unsaturated ester **2.11**.[104]

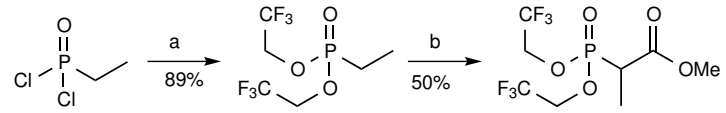


Scheme 2.5: Selectivity of the Still-Gennari reaction

The latter modification makes use of an α-branched phosphonoacetate under salt-free conditions to introduce the *Z*-olefin in 77% yield over 2 steps as a single diastereomer. In general, the phosphoryl-stabilized carbanion (**2.17**) attacks aldehyde **2.18** in a stepwise manner (scheme 2.5).[105] This leads to the oxyanion intermediates **2.19a** and **2.19b**, which can decompose to the olefin via a four-membered ring intermediate **2.20a** and **2.20b**. The *erythro* transition state **2.19b**, which precedes the formation of *Z*-olefin **2.21b**, is less sterically hindered, compared to the *threo* transition state **2.19b**, thus, under kinetic control, the former will prevail. However, the stereochemical outcome in the HWE-reaction is not only determined by the stereochemistry in the initial C-C bond forming step, but also by the possibility of the intermediates to do the reverse reaction. If the dissociation of the oxaphosphetane is slow, under thermodynamic conditions, an equilibrium can set in, and through rotation (**2.22**), the most stable isomer will be formed. This is prevented by the use of an electrophilic phosphonate (caused by the presence of

the trifluoroethyl groups), and strongly dissociating conditions (the K^+ counter ion of the base is trapped by a cryptand, so the anion is not stabilized), causing a rapid breakdown of the oxaphosphetane **2.20b**, resulting in the formation of *Z*-olefin.

The required α-branched phosphonoacetate is synthesized in two steps, starting by reacting ethylphosphonic dichloride (**2.23**) with trifluoroethanol. The anion of the resulting phosphonate **2.24** is then reacted with methylchloroformate to produce phosphonate **2.25** in variable yields.[106,107]



2.23 **2.24** **2.25**

a) CF_3CH_2OH, NEt_3, THF, RT; b) [i] BuLi, HMDS, THF, -78°C; [ii] Cl(CO)OMe

Scheme 2.6: Preparation of the α-branched phosphonoacetate

The geometry of the α,β-unsaturated ester **2.11** is proven using nuclear Overhauser effect spectroscopy (NOESY). This makes use of the dipolar interaction between nuclear spins to prove correlation between protons. The intensity of this nuclear Overhauser effect is approximately proportional to $1/r^6$, where r is the distance between two protons. Hence, only protons which are in close enough proximity (i.e. closer than 5Å) will show a signal in the NOESY spectrum. In this spectrum (figure 2.1) a crosspeak is visibile between vinylic proton 2 and the allylic methyl protons at position 1, whereas a crosspeak between protons at position 1 and 3 (in case of the *E*-geometry) is lacking.

The unsaturated ester is transformed to the aldehyde by DIBAH reduction to **2.12**, followed by Dess-Martin periodinane oxidation to **2.13**, in 95% yield over two steps. The resulting aldehyde is then subjected to a stereoselective Brown allylation,[108–113] to yield homoallylic alcohol **2.14** in 79% isolated yield.

The chiral allylating reagent (-)-B-allyl-diisopinocampheylborane **2.28** is prepared by hydroboration of (+)-α-pinene (**2.26**), followed by methanolysis, leading

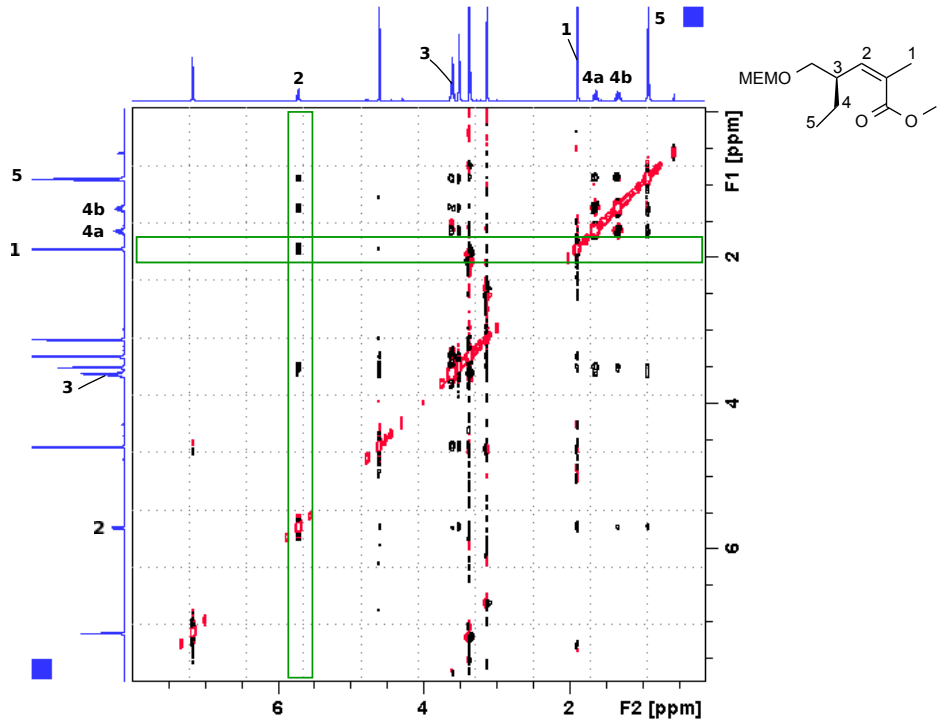
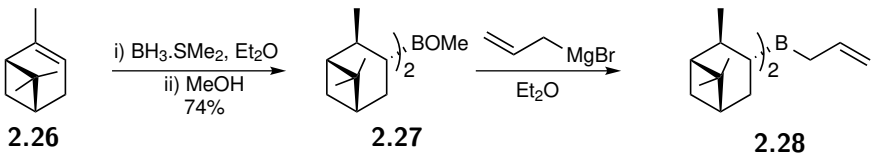


Figure 2.1: NOESY spectrum of **2.11**

to the corresponding dialkyl methoxyborane **2.27**. Upon treatment of the latter with allylmagnesium bromide, the requested allylborane is formed in high enantiomeric purity (figure 2.7). The boron atom acts as a Lewis acid in activating the aldehyde, while, at the same time, the aldehyde functions as a Lewis base, thereby increasing the nucleophilicity of the allylborane.



Scheme 2.7: Synthesis of (-)-B-allyldiisopinocampheylborane

The origin of stereoselectivity can be explained by a difference in transition state, where, in the unfavored mode of addition to the aldehyde, a steric interaction

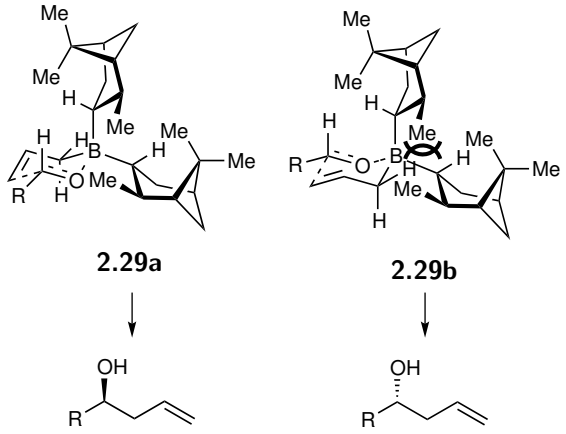


Figure 2.2: Origin of stereoselectivity in Brown's asymmetric allylation

between a methyl of one pinene group and the methylene of the allyl group causes an increase in energy (**2.29b**). This interaction is absent when the aldehyde is attacked from its other enantioface (**2.29a**) (figure 2.2).[114]

Verification of absolute stereochemistry *via* Mosher ester analysis

In order to determine the absolute configuration of the stereocenter formed during allylation, the Mosher method is applied. Mosher derived an empirical correlation between the configuration of a stereocenter and NMR chemical shifts of diastereomeric α-methoxy-α-trifluoromethylphenylacetate (MTPA) esters, and developed a model to rationalize this.[115,116]

First, the chiral, secondary alcohol must be converted into both diastereomeric MTPA derivatives. The ^{1}H-NMR spectra of the diastereomers with known configuration at the acid moiety, but unknown configuration at the carbinyl centre are then recorded and compared. The difference in chemical shift of the two diastereomers can be used to assign the absolute configuration of the carbinol. Based on experiments on molecules with known absolute configuration, Mosher developed a model which could account for this difference in chemical shift (Figure 2.3). To

rationalize this model, one should look at the conformation of each diastereomer in which the ester adopts the transoïd conformation around its O-(CO) bond, and in which both the α-trifluoromethyl substituent of the MTPA ester and the methine proton of the secondary alcohol are *syn*-coplanar. This should not be the ground-state conformations, but they are the most important conformation to explain the different spectroscopic behavior of the diastereomers. The phenyl group of the MTPA ester imposes an anisotropic magnetic shielding effect on protons that reside above or below the plane of this phenyl ring. This shielding results in a more upfield (lower ppm value) shift for the affected protons in the NMR spectrum. Consequently, the difference in chemical shift between the *R*-MTPA ester and the *S*-MTPA ester ($\delta^{RS} = \delta^{R}$-δ^{S}) will be negative for R^1 and positive for R^2.

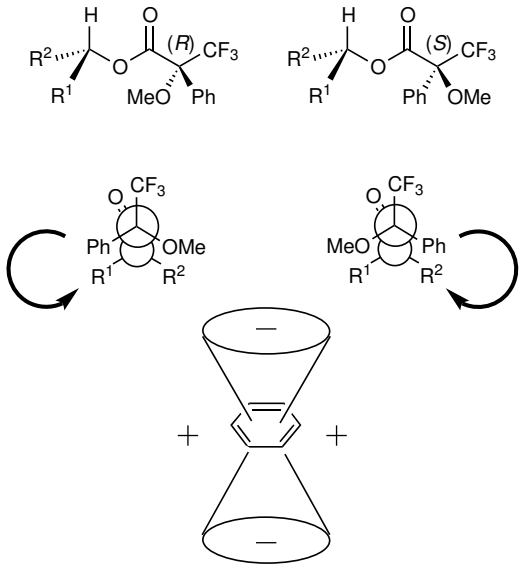
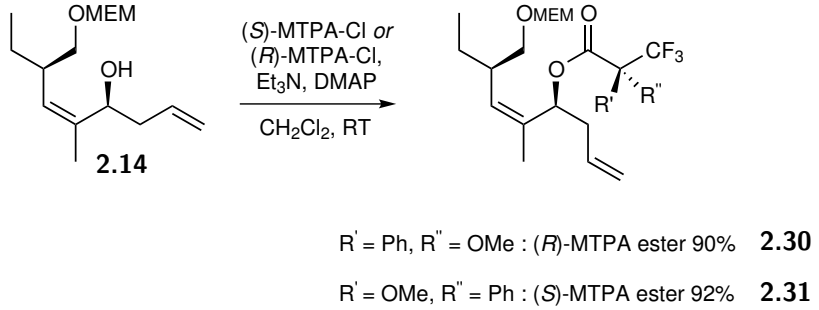


Figure 2.3: The Mosher model

Thus, by calculating the difference in chemical shift between corresponding pairs of protons in R^1, respectively R^2 for both diastereomeric MTPA-esters, the configuration of an unknown stereocenter can be assigned. [i]

[i]As the Mosher model is based on empirical results, it is not definitive proof of the absolute stereochemistry. However, it is a common tool in total synthesis to assign this.

Therefore, both R- and S- MTPA esters (**2.30** and **2.31**) were synthesized, using the corresponding (S)- and (R)- MTPA-chlorides (Scheme 2.8).



Scheme 2.8: Synthesis of the Mosher esters **2.30** and **2.31**

The difference in chemical shift between the (R)- and (S)- diastereomeric esters **2.30** and **2.31** (**2.32** in figure 2.4) most likely indicated the absolute configuration of **2.14** to be S.

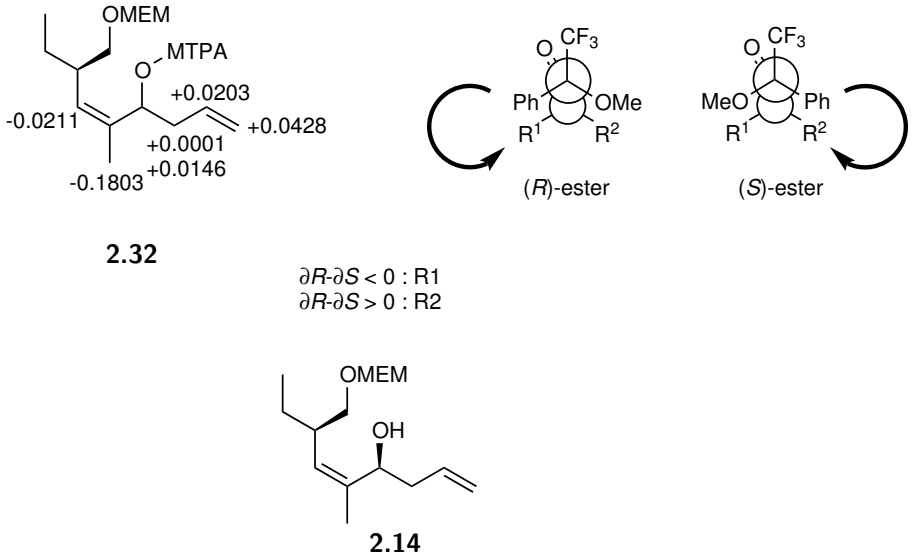
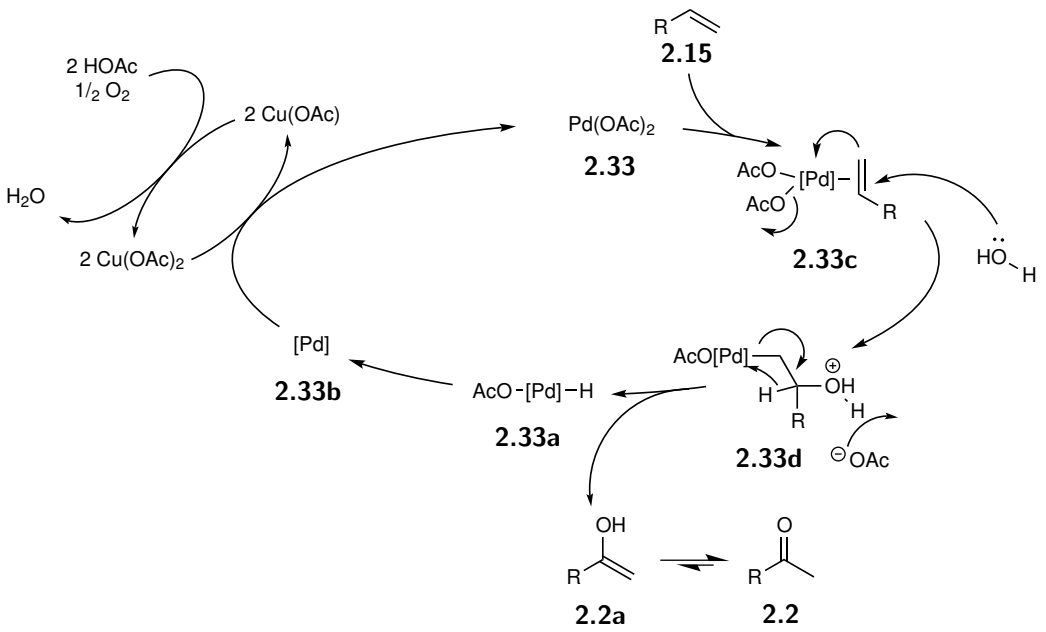


Figure 2.4: The Mosher model applied to **2.14**

The new homoallylic alcohol **2.14** was protected as MPM ether. This protecting group can be selectively cleaved, which is necessary to close the macrocycle

later on in the synthesis. Standard conditions including deprotonation with NaH and reaction with MPM chloride in the presence of TBAI afforded **2.15** in 96% yield. In a final step, the terminal alkene in **2.15** was converted to the corresponding methyl ketone. This was achieved using Wacker-Tsuji conditions: a Pd(II)-catalyzed process in which the reacted Pd(0) is reoxidized by addition of an external oxidant, in this case $Cu(OAc)_2$.[117] In the catalytic process (scheme 2.9), complexation of the alkene to Pd(II) makes it susceptible for nucleophilic attack. The attack mainly happens at the more substituted position, as the developing positive charge is better tolerated at the secondary position compared to the primary. This results in the formation of a σ-alkyl Pd-complex, which can rapidly undergo β-hydride elimination to enol **2.2a**, which tautomerizes to the corresponding ketone **2.2**. The remaining Pd-complex **2.33a** will undergo a reductive elimination, resulting in a Pd(0)-species **2.33b**, which needs to be reoxidized. This is achieved by the external oxidant, $Cu(OAc)_2$, which in turn is reduced to a Cu(I) species (Cu(OAc)). By performing the reaction under an oxygen atmosphere, the Cu(I) species can be reoxidized to Cu(II) with formation of water, so in principle, catalytic amounts of $Cu(OAc)_2$ are sufficient.[118]

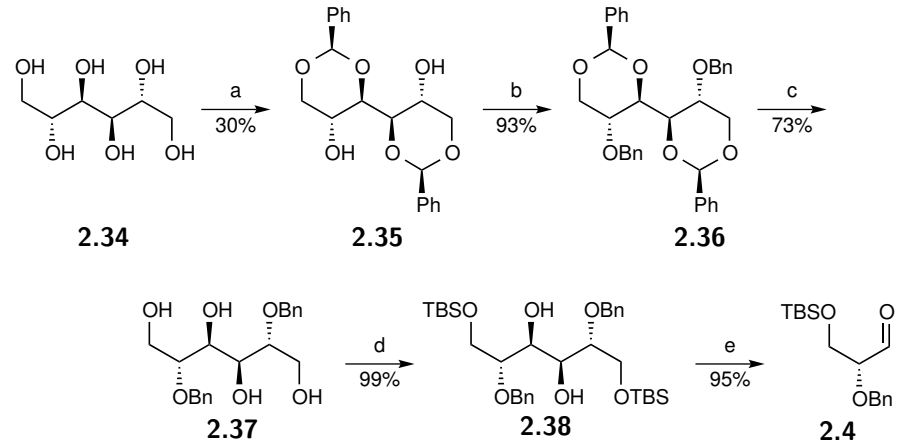


Scheme 2.9: Catalytic cycle of the Wacker-Tsuji oxidation

2.3 Synthesis of the C_1-C_3 fragment 2.4

The synthesis of aldehyde **2.4** is based on the chiral pool approach, starting from D-mannitol (**2.34**). First, the regioselective protection of the 1,3- and 4,6-diols as benzylidene acetals (**2.35**) was achieved under sulphuric acid catalysis. The modest yield (30%) is explained by the formation of different regioisomers, as shown by LC-MS analysis.[119] From here on, the synthesis was mainly described by Reetz *et al.*.[120] However, this procedure proved to be not reproducible, and thus, optimization was necessary. Benzylation of the resulting secondary alcohols in **2.35** was achieved by combining benzyl bromide with a KOH-solution in DMSO.[121] The advantages of this procedure are that it can be performed at room temperature and that special precautions against ingress of moist, such as using dry DMSO or performing the reaction under inert atmosphere are not necessary.

The subsequent cleavage of the benzylidene acetals in **2.36** was accomplished by acid catalyzed methanolysis in a biphasic mixture of methanol and hexane,[122] rendering tetrol **2.37**. Next, the primary alcohols had to be selectively protected.



a) PhCHO, H_2SO_4, DMF, RT; b) KOH, DMSO, BnBr, RT c) HCl, MeOH/C_6H_{14} 5/3, RT; d) TBSCl, imidazole, CH_2Cl_2, RT; e) $NaIO_4$, THF/H_2O 4/1, RT

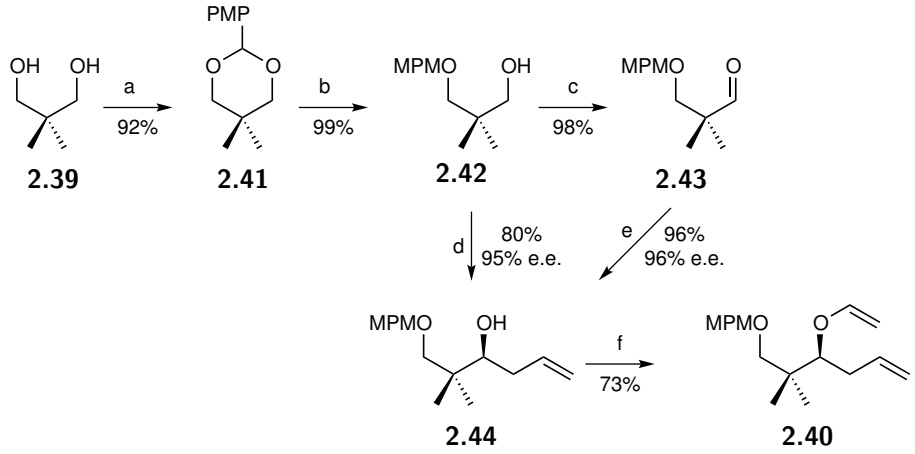
Scheme 2.10: Synthesis of the C_1-C_3 aldehyde

The reported procedure (NEt_3, DMAP)[120] did not prove effective enough as the reaction did not proceed to completion, even after prolonged reaction times. Performing the reaction in CH_2Cl_2 with imidazole as a base, however proved very effective, as the reaction was finished within one hour, providing the bis-TBDMS ether **2.38** in 99% yield.

The final step to obtain the first building block, the oxidative cleavage of the resulting diol **2.38** with sodium periodate, proceeded smoothly in 95% yield, resulting in two molecules of aldehyde **2.4**, with the correct stereochemistry at C_2.

2.4 Synthesis of the C_4-C_{11} bisnucleophile 2.5

As 2,2-dimethyl-1,3-propanediol (neopentylglycol, (**2.39**), scheme 2.11) already contains the *gem*-dimethyl unit present in the bisnucleophile, it is an ideal starting point for the synthesis of **2.40**. Protection and oxidation then sets the stage for stereoselective allyl addition, and subsequent vinylation of the resulting homoallylic alcohol.



a) 4-MeO-PhCH(OMe)$_2$, CSA, CH_2Cl_2, RT; b) $LiAlH_4$, $AlCl_3$, Et_2O, -10°C; c) [i] $(COCl)_2$, DMSO, -78°C [ii] Et_3N, CH_2Cl_2, -78°C; d) $[Ir(cod)Cl]_2$, (*S*)-(-)-Cl, MeO-BIPHEP, Cs_2CO_3, 4-Cl-3-NO_2-benzoic acid, THF, allylOAc, 120°C; e) $[Ir(cod)Cl]_2$, (*S*)-(-)-Cl, MeO-BIPHEP, Cs_2CO_3, 4-Cl-3-NO_2-benzoic acid, THF, allylOAc, 2-PrOH, 120°C; f) $Hg(CF_3COO)_2$, $EtOCHCH_2$, RT

Scheme 2.11: Synthesis of the MPM protected C_4-C_{11} enol ether

As there was already a benzyl protecting group present in the aldehyde building block **2.4**, the choice fell on the use of a p-methoxy benzyl protecting group, which could be orthogonally removed later in the synthesis. It was opted to monoprotect the original diol in a two-step procedure, as experience in the lab for the monobenzylation of this diol had shown that this could be achieved in high yields and without intermediate purification.[123]

Herefore, the diol was protected as acetal (**2.41**), making use of p-methoxy benzyl dimethyl acetal and CSA. In a first attempt, it was used for the next reaction without further purification. For the reduction, a combination of $LiAlH_4$ and equimolar portions of $AlCl_3$ was used. In this case, AlH_2Cl is formed, according to the equation $AlCl_3 + LiAlH_4 \rightleftharpoons 2\,AlH_2Cl + LiCl$, which was shown to be the active species in the reduction of the acetal.[124]

In a third, consecutive step, Swern conditions were applied to oxidize the alcohol **2.42** to aldehyde **2.43**. After purification, minor amounts of *p*-methoxy benzaldehyde were isolated, originating from the excess of *p*-methoxy benzyl dimethyl acetal which was used in the first step, and which was respectively reduced and

oxidized again. As this impurity was complicating the separation after the oxidation, it was decided to repeat the synthesis with purification after every step. In this way, the yields (91% over 3 steps) and the ease of separation were improved.

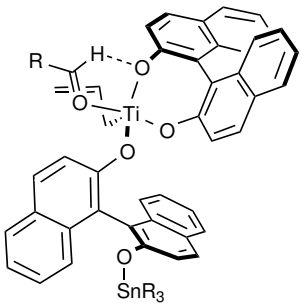
Having aldehyde **2.43** in hand, the stereoselective allylation was the next step. Several conditions were tested (table 2.1) and the best one was selected, based on the highest enantiomeric excess. This was determined by chiral LC. A first method (entry 1) made use of stoichiometric amounts of the chiral allylating reagent (−)-B-allyldiisopinocampheylborane **2.28**, as described before (scheme 2.7). The selectivity of the reaction with this chiral reagent was however lower than expected (table 2.1, entry 1). Moreover, purification of the reaction was laborious, because of the abundant side products. Therefore, our attention turned to catalytic systems, making use of a Lewis acid in combination with a chiral ligand.

Entry	catalyst	ligand	allyl donor	T	e.e.	yield
1	none	none	(−)-$(ipc)_2$Ballyl	-78°C	30%	n.d.
2	Ti(iPrO)$_4$	(S)-BINOL	allylSnBu$_3$	-20°C	41%	n.d.
3	TiF$_4$	(S)-BINOL	allylSiMe$_3$	0°C	84%	n.d.
4	[Ir(cod)Cl]$_2$	(S)-MeO,Cl-BIPHEP	allylOAc	120°C	96%	96%

Table 2.1: Allylation conditions (n.d.: not determined)

In this respect, the catalytic asymmetric allylation reaction, designed by G.E. Keck in 1993, is a useful method.[125] According to Corey, by combining two equivalents of the chiral (R)- or (S)- BINOL ligand with one equivalent of Ti(iOPr)$_4$, a bis-BINOL titanate ester ((BINOL)$_2$Ti) is generated, which makes up the catalytic species.[126,127] On the basis of this two ligand model (figure 2.5), Corey proposed that a transmetallation occurs, when the allylstannane reacts with the (BINOL)$_2$Ti complex, resulting in an allyl-Ti(IV) complex where the trialkyltin group is attached to one of the BINOL oxygens, upon which this oxygen dissociates

from titanium. Coordination of the aldehyde then occurs, according to Corey's model, in such a way that a hydrogen bonding interaction can emerge between the formyl hydrogen and one of the oxygens of the BINOL ligand, thereby forming a trigonal bipyramidal structure (**2.45**, figure 2.5). In this arrangement, the non-bonding steric repulsions are minimized and the allyl group is placed in a basal position, whereas the formyl O is based in an apical position, which is ideal for the allylation to occur. Thus, according to the proposed model, based on a formyl hydrogen bond, the (*S*) configuration of the homoallylic alcohol stems from (*S*)-BINOL and *vice versa*. It should be noted that this is only a working model, which provides a rationale for the observed enantioselectivity, but too little is known to provide the real origin of asymmetric induction.

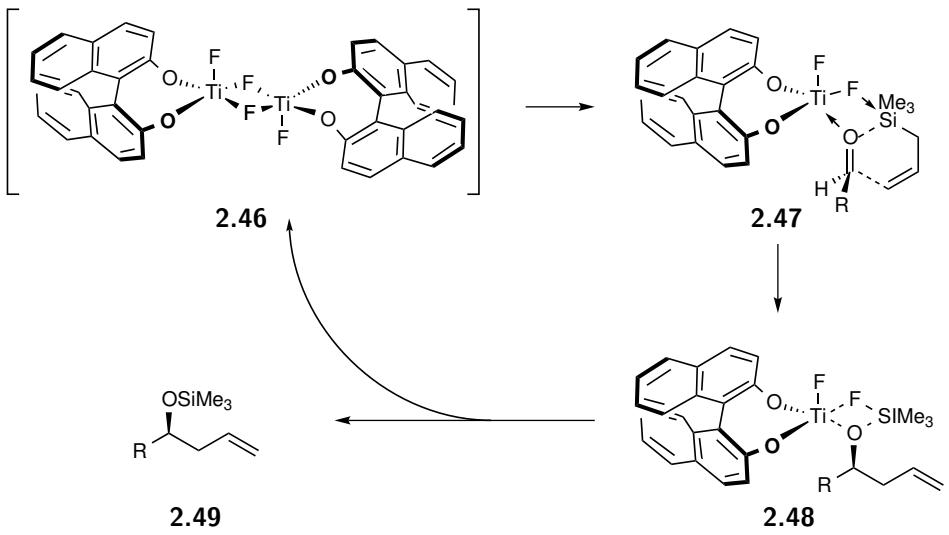


2.45

Figure 2.5: Corey's proposal for a transition-state structure in the Keck allylation.

As the optical purity using the Keck method was also disappointing (table 2.1, entry 2), another catalytic system, developed by Carreira was tested (entry 3, table 2.1). This method is known to be particularly effective for the enantioselective allylation of hindered, aliphatic, non-enolizable aldehydes.[128,129] The catalytic system makes use of TiF_4 as catalyst in combination with the chiral BINOL ligands, and non toxic allylsilanes as allyl donor. In general, Ti(IV)/BINOL catalysts are too weak Lewis acids for the allylation with less nucleophilic allylsilanes. However, due to the increased electronegativity of fluorine, TiF_4 is an exception. Furthermore, the fact that a Ti-F bond is stronger than a Si-F bond may assist in catalyst turnover.

^{1}H-NMR experiments showed formation of propene and Me_3SiF upon mixing of the TiF_4-BINOL complex with allyltrimethylsilane, suggesting that the latter originally acts as a base to neutralize the formed HF during the catalyst preparation. Moreover, the formation of an allyltitanium species was not visible, indicating that a transmetalation as suggested by the Corey model in the Keck allylation, is not occuring. In terms of stereochemical outcome, however the model is still valid, as the (*S*)-BINOL ligand produces the (*S*)-enantiomer. Duthaler proposed a transition state where the electrophilic Ti center activates the aldehyde, and simultaneously, the fluoride complexes the silicium of the allylsilane, hereby increasing the reactivity of the latter.[130,131] This could then directly produce the silylated homoallylic alcohol, with regeneration of the catalyst.



Scheme 2.12: Catalytic cycle for the enantioselective allylation using TiF_4, as proposed by Duthaler[130]

The outcome of this test reaction in terms of enantioselectivity was better than the previous ones (table 2.1, entry 3), however, as there was still room for improvement, another method was tested.

In 2008, Krische *et al.* reported on a novel enantioselective, iridium-catalyzed allylation method, via transfer hydrogenative coupling of allyl acetate.[132,133] The optimized catalytic system employs $[Ir(cod)Cl]_2$ as iridium source, together with a chelating phosphine ligand and cesium *m*-nitrobenzoate as an additive. Different test reactions suggested that *m*-nitrobenzoate and the iridium center must be closely associated during the enantioselective addition. Therefore, the group of Krische was able to isolate a catalytically relevant complex, using (*R*)-BINAP as a ligand. A single-crystal x-ray diffraction experiment revealed the presence of an ortho-cyclometalated iridium(III) - π allyl complex (Figure 2.6). Despite its stability, this complex is considered to be the active catalyst, based on the use of the isolated complex, instead of its *in situ* generation, which gives better results.

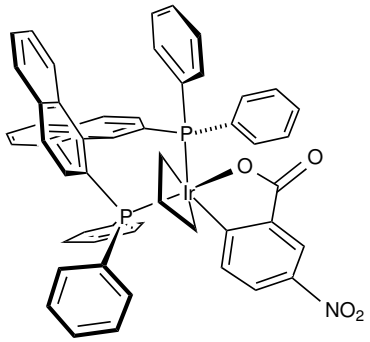
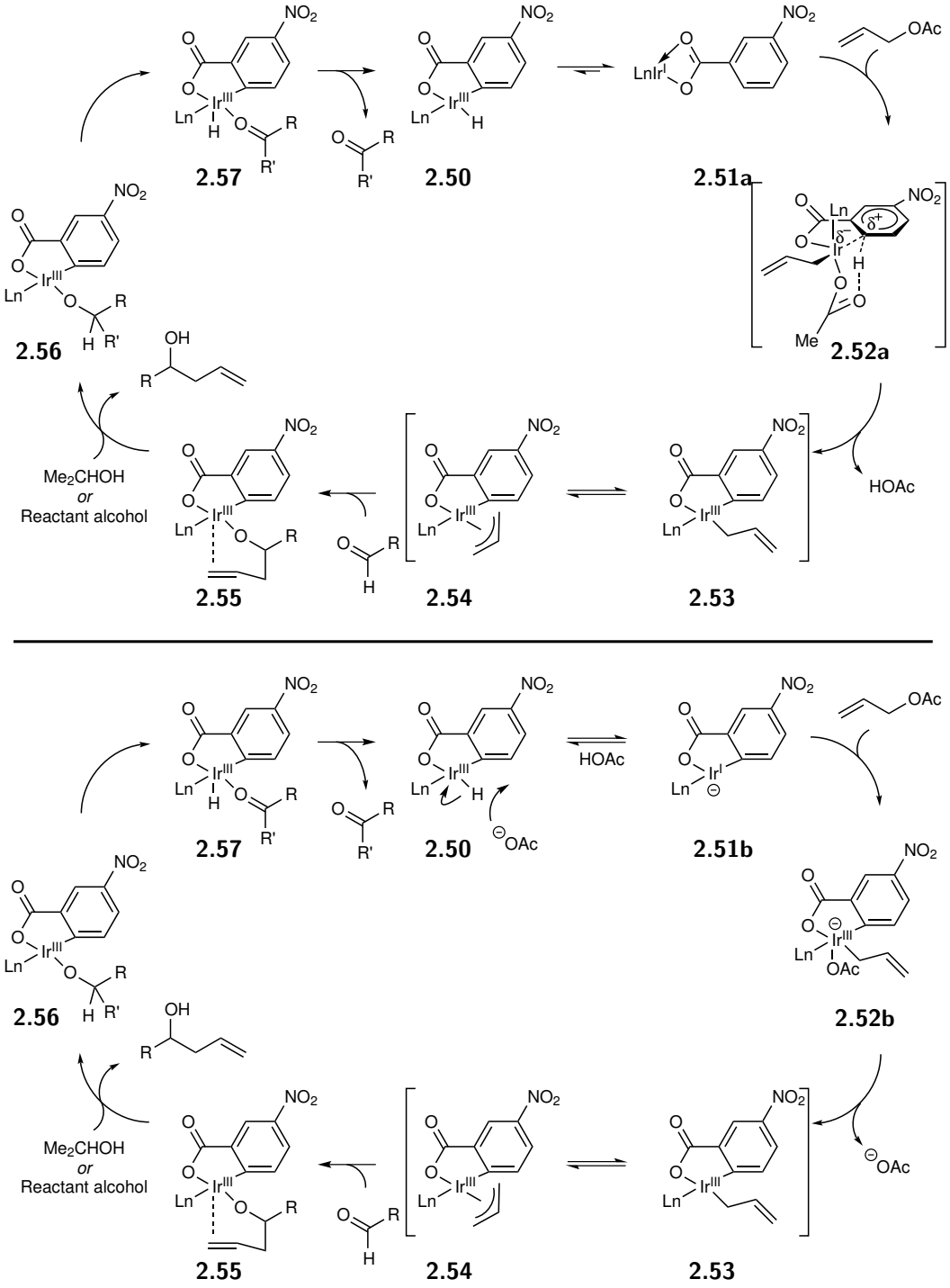


Figure 2.6: Catalytically active ortho-cyclometalated iridium(III) - π-allyl complex, as determined by single X-ray diffraction analysis.[133]

Very remarkable is that this method promotes carbonyl allylation both from the aldehyde as from the alcohol oxidation level. In the former case, isopropanol is added as hydrogen donor, in the latter case, the alcohol acts both as aldehyde precursor and reducing agent.

Based on the observations, Krische proposed two possible catalytic cycles.[133] In a first one (scheme 2.13, upper half), the iridium carboxylate **2.51a**, which is in equilibrium with ortho-cyclometalated complex **2.50**, undergoes oxidative addition and then can undergo acetate-assisted ortho-metalation through the six-membered transition structure **2.52b**. This results, after loss of acetic acid, in the

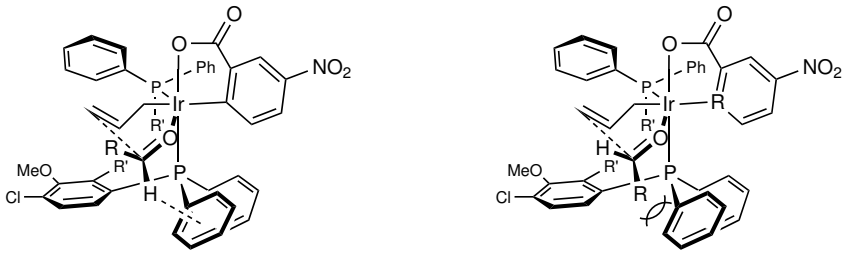
formation of σ-allyl C,O-benzoate complex **2.53**, which can rapidly equilibrate with the corresponding π-allyl haptomer **2.54**, of which the X-ray structure was confirmed. Extra evidence for this equilibrium was provided by performing the allylation with isotopically labeled allyl acetate (CH_2CHCD_2OAc), which resulted in equimolar amounts of the deuterio and isodeuterio homoallylic alcohols. The allyl group is then transferred to the aldehyde, resulting in the homoallyl iridium alkoxide **2.55**. In this step, β-hydride elimination is probably prevented by coordination of the olefin of the formed alcohol. On the other hand, when the homoallylic alcohol is exchanged for a reactant alcohol or for isopropanol (in the case where the aldehyde is used as the allylation substrate), β-hydride elimination can occur, forming complex **2.57**. The starting complex **2.50** is then regenerated by dissociation of the resulting aldehyde, upon which the cycle is complete.



Scheme 2.13: Proposed catalytic cycles for the iridium catalyzed allylation. (Ln = Cl,MeO-BIPHEP)[133]

Also the second possible pathway is in agreement with the observations (scheme 2.13, lower half). Here, the cyclometalated system stays intact during the complete cycle. Proton loss from the originally cyclometalated complex **2.50** is assisted by the stabilization of the new anion (iridium (I) benzoate **2.51b**) by the carboxylate and the electron withdrawing groups thereon. Oxidative addition of allyl acetate results in the anionic Ir(III) σ-allyl complex **2.52b**, which can loose the acetate to form the same active species as in the first proposal. The rest of the catalytic cycle is consequently identical.

Based on the coordination mode which was revealed in the X-ray structure of **2.54**, a stereochemical model which accounts for the observed induction was proposed (figure 2.7). In complex **2.53**, the aldehyde is positioned in such a way, that it occupies the biggest open space. The allyl group however is placed between the bisaryl and the phenyl moieties of the ligand. This creates a favored mode of addition, in which the aldehyde's formyl hydrogen is projected into the π-face of a phenyl moiety of the ligand. This causes a weakly attractive C-H – π interaction, an interaction which is also sometimes observed in peptide folding.[134,135] On the other hand, in the disfavored mode of addition, the R group of the aldehyde projects in the π-face of a phenyl moiety of the ligand, giving rise to a strong steric interaction.



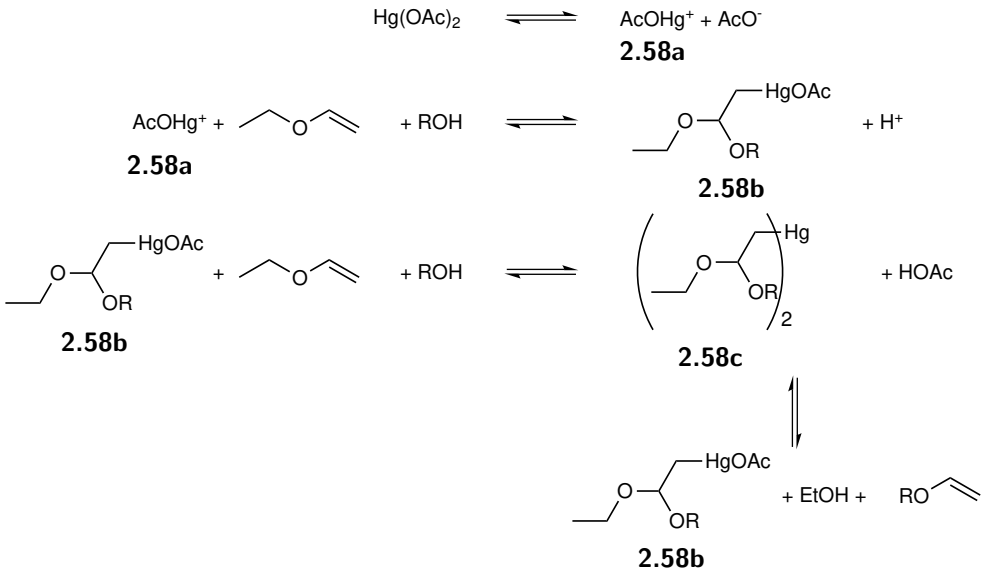
2.53 *favored* **2.53** *disfavored*

Figure 2.7: Proposed stereochemical model accounting for the observed stereoinduction in the iridium catalyzed allylation. Part of the Cl,MeO-BIPHEP ligand (R'-R') is omitted for clarity.[133]

Using this method, starting from the alcohol as a substrate, the yield of **2.44**

was 80% and the e.e. 94%, whereas, starting from the aldehyde, both yield and e.e. were 96%.

The final step in the synthesis of the C_4-C_{11} fragment, the vinylation of the homoallylic alcohol **2.44**, was accomplished under mercury catalysis (scheme 2.11). In 1956, Watanabe and Conlon reported on the preparation of vinyl ethers *via* transetherification of commercially available alkylvinyl ethers.[136] Their research revealed that mercury salts are highly specific catalysts in doing this, whereas other metals were mainly inactive. The proposed reaction mechanism with $Hg(OAc)_2$ is in essence a reversible alkoxymercuration, where the equilibrium is shifted by using a large excess of the alkylvinyl ether.



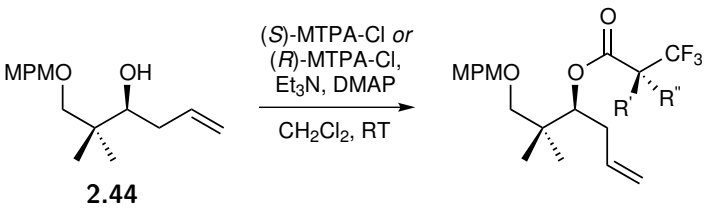
Scheme 2.14: Proposed reaction mechanism for the mercury catalyzed vinylation[136]

After dissociation of the mercuric salt (scheme 2.14), the vinyl group is activated by the formed cation **2.58a**, upon which the reactant alcohol can attack and intermediate **2.58b** is formed. Further dissociation of the salt opens the possibility for an identical addition of the reactant alcohol, resulting in diacetal **2.58c**. This hypothesis originated from the ability of the original authors to synthesize and

isolate intermediates like **2.58b**, R being methyl or ethyl. These isolated species, in the absence of acid, proved to be also catalytically active. Later, the actual formation of intermediate **2.58b** during the reaction itself was shown.[137] There is however no direct evidence for the formation of an intermediate like **2.58c** in the reaction mixture, however, when adding a base to the mixture, the acetic acid is precipitated as salt, shifting the equilibrium to the formation of **2.58c** (as proven by NMR), and the catalyst is inactivated.[137]This means a proton from the formed acetic acid is necessary to decompose intermediate **2.58c** and get the desired vinyl ether.

For the vinylation of **2.44** to **2.40** (scheme 2.11), when using $Hg(OAc)_2$ in ethylvinyl ether, the reaction did not run to completion. However, when changing the catalyst to $Hg(CF_3COO)_2$, **2.40** was formed in 73%, after 3 days. This vinylation occurred without loss of optical purity, as verified by chiral LC.

Once again, the absolute stereochemistry of this center was assigned using Mosher ester analysis. After synthesizing the (*R*)- and (*S*)-MTPA esters of the homoallylic alcohol **2.44**, the ^{1}H NMR spectra were recorded. The difference in chemical shift between corresponding signals of the (*R*)- and (*S*)-ester (**2.59**) is depicted in figure 2.8. From the analysis of Mosher's model, it appeared that the wrong enantiomer was obtained (**2.60**). This was caused by a mistake of the chemical supplier who had sold the (*R*)-Cl,MeO-BIPHEP ligand under the name of its enantiomer. Pursuing the synthesis with the correct (*S*)-ligand delivered the opposite (envisaged) enantiomer, as confirmed by chiral LC.



2.44

R' = Ph, R" = OMe : (*R*)-MTPA ester 89% **2.61**

R' = OMe, R" = Ph : (*S*)-MTPA ester 81% **2.62**

Scheme 2.15: Synthesis of the Mosher esters **2.61** and **2.62**

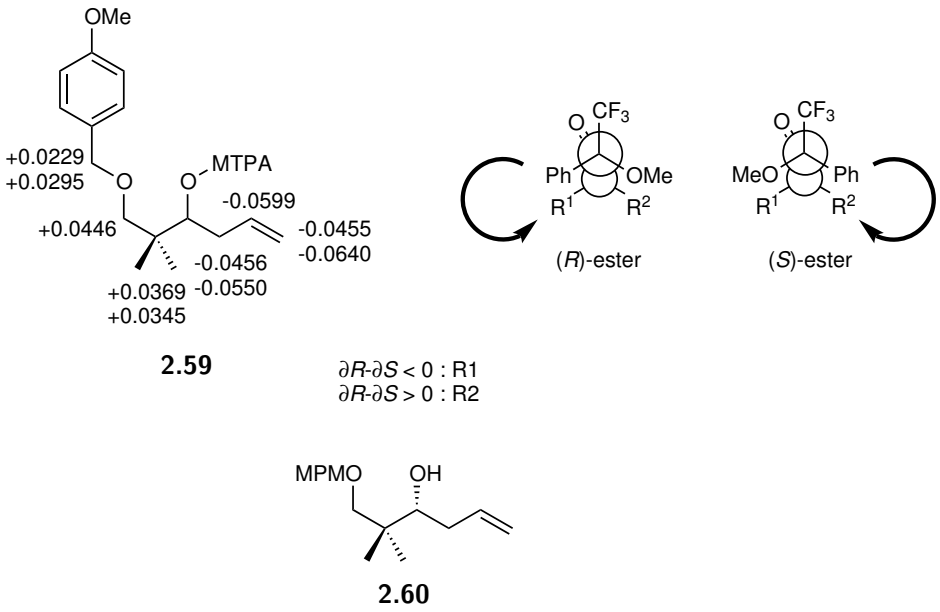
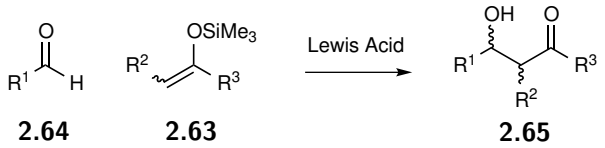


Figure 2.8: The Mosher model applied to **2.44**

2.5 The Mukaiyama aldol - Prins cyclization (I)

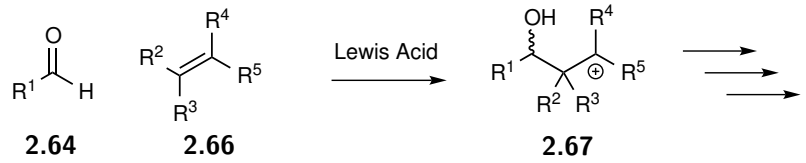
The Mukaiyama aldol - Prins cyclization is a cascade or domino reaction between an aldehyde and a bisnucleophile. According to Tietze, a cascade reaction is defined as follows: *"A cascade reaction is a process in which two or more bond-forming transformations occur based on functionalities formed in the previous step. Furthermore, no additional reagents, catalysts, or additives can be added to the reaction vessel, nor can reaction conditions be changed."*[138] In this case, the two bond forming transformations are a Mukaiyama aldol reaction and a Prins reaction.

The Mukaiyama aldol reaction in general is a Lewis acid catalyzed nucleophilic addition of an enol silyl ether **2.63** to a carbonyl compound **2.64**, thereby generating one C-C bond, resulting in a β-hydroxy carbonyl compound (**2.65**) (scheme 2.16). The aldol reaction is one of the most important C-C bond forming reactions in organic synthesis.



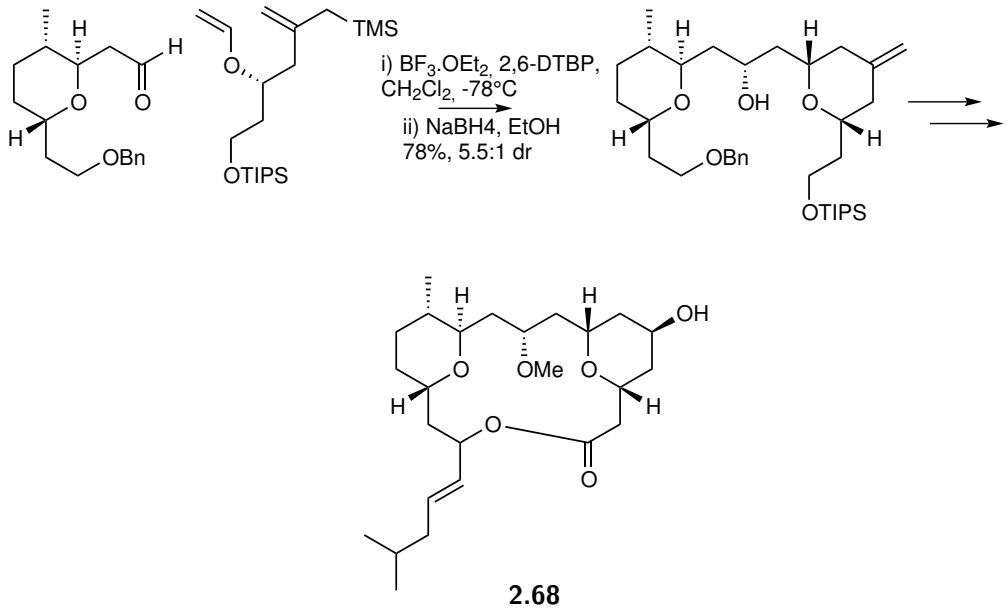
Scheme 2.16: The Mukaiyama aldol reaction

The Prins reaction in general is a nucleophilic addition of an alkene **2.66** to an activated carbonyl compound **2.64** (scheme 2.17). Starting from the resulting carbocation **2.67** and dependent on the reaction conditions and the nature of the alkene, different products can be formed.



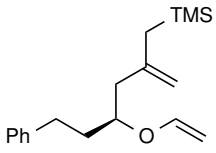
Scheme 2.17: The Prins reaction

The Mukaiyama aldol - Prins cascade reaction was first reported in 2001 by Rychnovsky, for the formal total synthesis of Leucascandrolide A (**2.68**, scheme 2.18).[139] It was known that electrophilic additions of alkyl enol ethers could be problematic because the intermediate oxocarbenium ion **2.69** (scheme 2.19) is very reactive and can produce oligomers by reacting with the starting enol ether. In order to avoid this, they came up with the idea of introducing a second nucleophilic group into the enol ether that is reactive enough to trap the oxocarbenium ion and by consequence to produce a new ring. When this second nucleophile is an alkene (**2.70**), the trapping reaction becomes a Prins cyclization. The remaining carbocation in **2.71** can then be trapped by an external nucleophile. At first, the only so-called bisnucleophile, which was reactive enough to prevent oligomerization, was the allylsilane **2.72** (figure 2.9). Using this allylsilane, MAP reactions with a variety of aldehydes were performed in good yield, but without significant facial selectivity in aldehyde addition.[139]



2.68

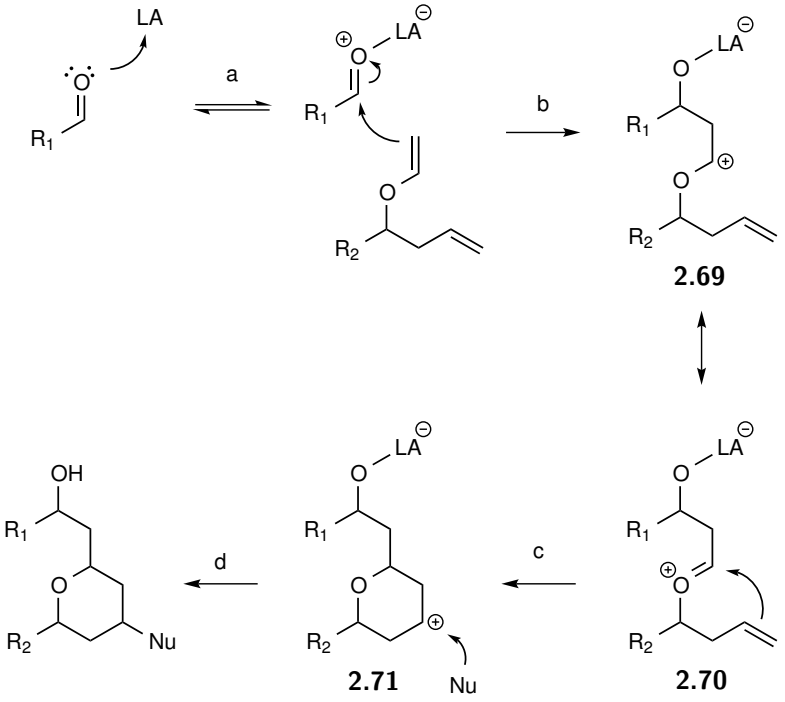
Scheme 2.18: First application of the Mukaiyama aldol - Prins cyclization, for the synthesis of Leucascandrolide A **2.68**[139]



2.72

Figure 2.9: Allylsilane **2.72**

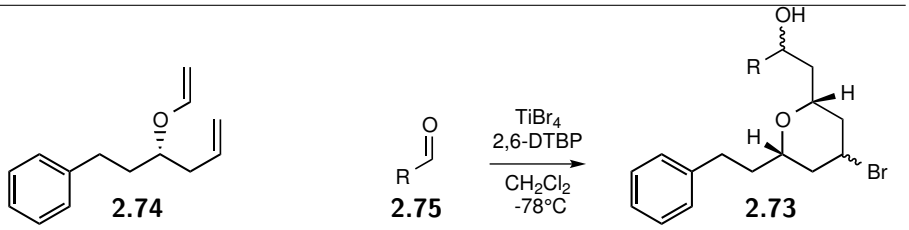
Later, Rychnovsky proved that it was possible to perform the MAP reaction using simple, easier-to-synthesize, alkenes, by choice of an appropriate Lewis acid.[99] The use of $TiBr_4$ proved the most effective, and led to the 3-bromo-2,6-*cis* substituted tetrahydropyran **2.73a** as a 1:1 mixture of diastereomers at the alcohol epimeric centre, but with a selectivity for the equatorial bromide (>95:5) (table 2.2, entry 1). Testing the scope of the reaction, Rychnovsky came up with some interesting results concerning the stereochemistry, when using the aldehydes with protected alcohols. A first observation was that, when using a TBDPS-protecting group at the β-position of the aldehyde, the behavior is identical to an aliphatic



Scheme 2.19: General mechanism for the Mukaiyama aldol - Prins cyclization

aldehyde, with a strong selectivity for the equatorial bromide (entry 2). A benzyloxy group at this position, however, showed an increase in the formation of axial bromide (entry 3). Also, when this benzyloxy group was present at the α-position of an enantiomerically pure aldehyde, there was an increase in formation of axial bromide (entries 4-5). At the same time, however there was a strong selectivity for the alcohol stereogenic centre, in favor of the *syn*-product (>95:5), regardless of the absolute stereochemistry of the α-chiral center of the aldehyde. On the other hand, in case of a silyl-protecting group at this α-position of the aldehyde, the stereoselectivity for the alcohol center dropped again (entry 6). The origin of selectivity at the carbinol was thought to be chelation-controlled, where there has been no conclusive explanation for the origin of the selectivity at the bromide center.

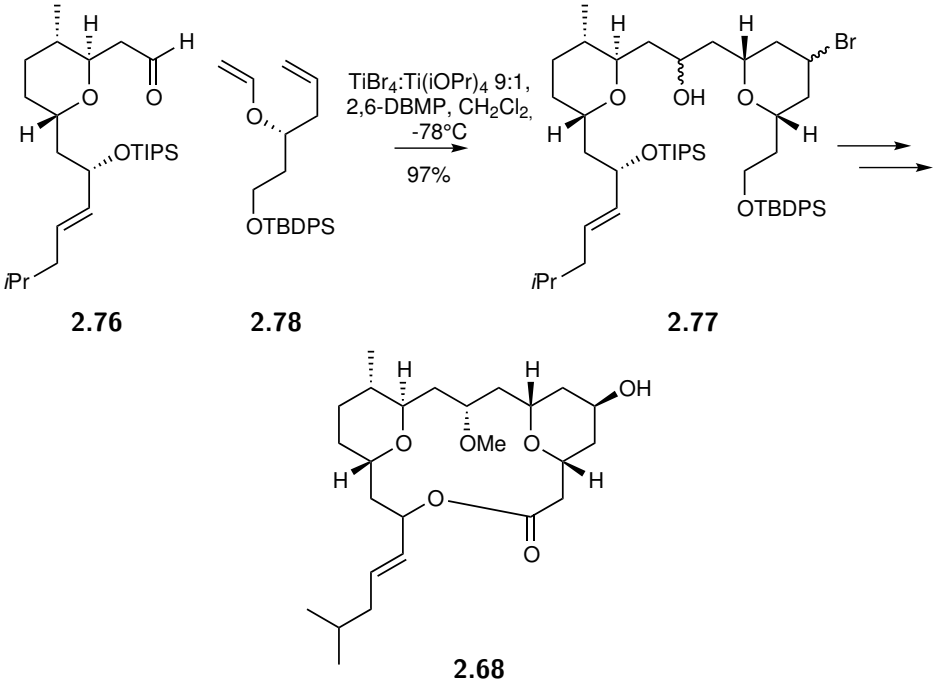
Also this new approach, using a simple homoallylic alkyl enol ether **2.78** and $TiBr_4$, proved successfully for the synthesis of Leucascandrolide A (scheme



Entry	enol ether	aldehyde	product	dr(OH)	eq/ax
1	**2.74**	**2.75a**	**2.73a**	1.1:1	>95:5
2	**2.74**	**2.75b**	**2.73b**	1.2:1	>95:5
3	**2.74**	**2.75c**	**2.73c**	1:1	68:32
4	**2.74**	**2.75d**	**2.73d**	>95:5	68:32
5	**2.74**	**2.75e**	**2.73e**	>95:5	66:34
6	**2.74**	**2.75f**	**2.73f**	68:32	>95:5

Table 2.2: Selected literature examples of MAP cyclizations

2.20).[140] In this case, using a β-alkoxy aldehyde (**2.76**, a 1,3-*anti*-relationship was observed between the β-alkoxy group and the new alcohol (**2.77**), probably originating from chelation-controlled addition (7.8:1 *anti:syn* for the axial bromide (53% yield), 4.5:1 *anti:syn* for the equatorial bromide (44% yield)).



2.76 **2.78** **2.77**

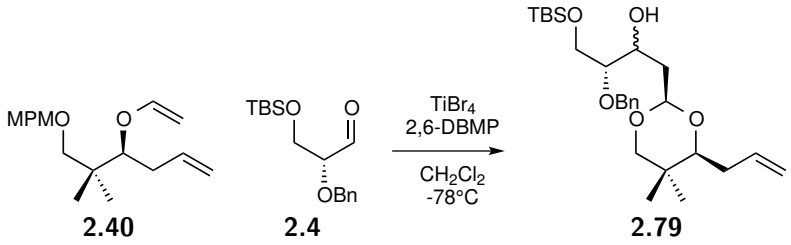
2.68

Scheme 2.20: $TiBr_4$-catalyzed Mukaiyama aldol - Prins cyclization, for the synthesis of Leucascandrolide A **2.68**[140]

Based on these literature results, we reasoned to have the perfect aldehyde coupling partner in hand, where an α-substituent is available for chelation and a bulky group at the β-position prevents chelation, thereby inducing the correct stereochemistry at C_3.

In a first attempt to synthesize the tetrahydropyran ring, we combined enol ether **2.40** with aldehyde **2.4** in the presence of 2 equivalents of $TiBr_4$ and 2,6-di-*tert*butyl-4-Me-pyridine (DBMP) as bulky base. Unfortunately, the expected cyclization did not occur. On the contrary, acetal **2.79** was formed, in 80% yield as

a diastereomeric mixture at the alcohol center (ratio 1.5:1). A possible explanation for the formation of this structure is that the Mukaiyama aldol is effective, thereby forming the required oxocarbenium ion, but instead of this cation being caught by the alkene, the MPM protected alcohol interferes (**2.79a** in figure 2.10). Cleavage of this protecting group is then triggered by complexation of the benzylic oxygen with the oxocarbenium ion as a Lewis acid.



Scheme 2.21: First attempt on the Mukaiyama aldol - Prins cyclization

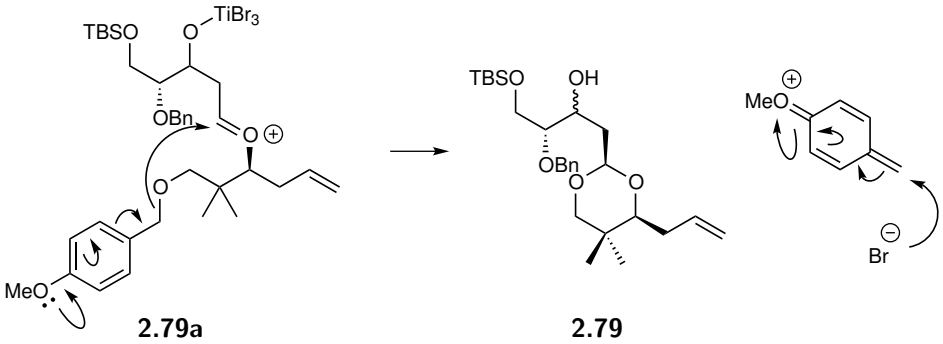
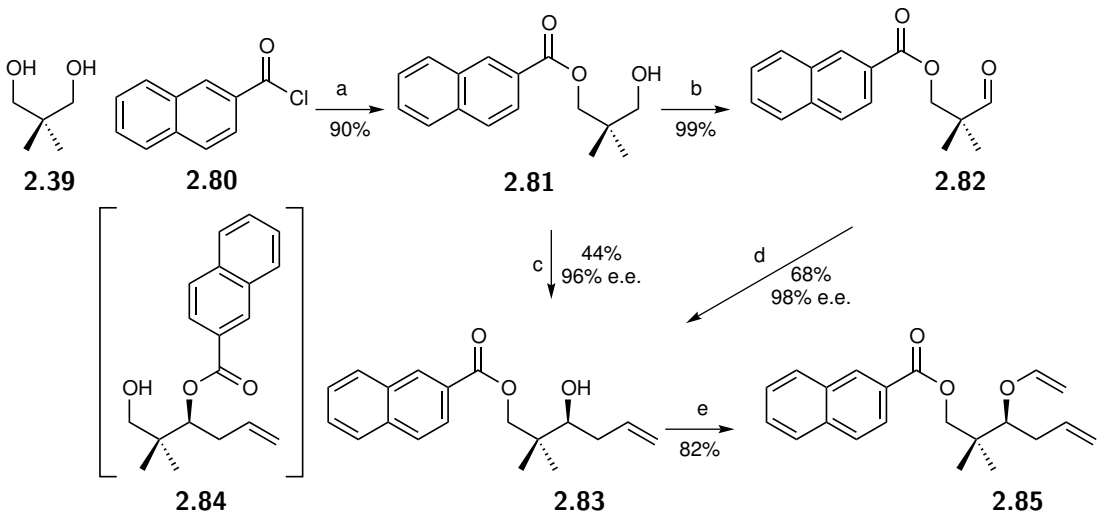


Figure 2.10: Presumed mechanism for the formation of acetal **2.79**

Encouraged by these first results, it was decided to change the nature of the protecting group of the alcohol at C_{11}. Using an ester protecting group would reduce the electron density, thereby lowering the chance of this oxygen to trap the oxocarbenium ion during Prins cyclization.



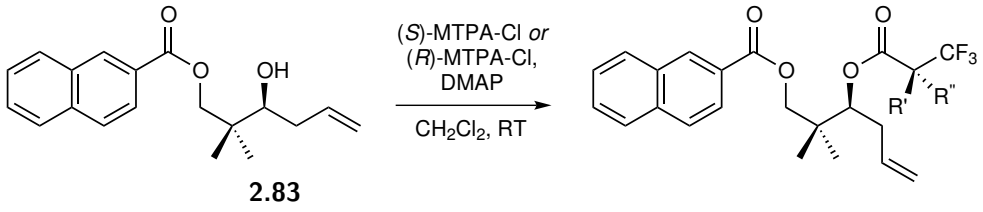
a) DMAP, NEt_3, CH_2Cl_2, RT; b) [i] $(COCl)_2$, DMSO, -78°C [ii] Et_3N, CH_2Cl_2, -78°C; c) $[Ir(cod)Cl]_2$, (*S*)-(-)-Cl, MeO-BIPHEP, Cs_2CO_3, 4-Cl-3-NO_2-benzoic acid, THF, allylOAc, 120°C; d) $[Ir(cod)Cl]_2$, (*S*)-(-)-Cl, MeO-BIPHEP, Cs_2CO_3, 4-Cl-3-NO_2-benzoic acid, THF, allylOAc, 2-PrOH, 120°C; e) $Hg(CF_3COO)_2$, $EtOCHCH_2$, RT

Scheme 2.22: Synthesis of the ester protected C_4-C_{11} enol ether

2.6 Synthesis of the C_5-C_{11} bisnucleophile 2.85

As a napthoyl ester had already proven to be compatible with the required MAP conditions,[141] it was implemented in our synthesis (scheme 2.22). In a first step, 2,2-dimethyl-1,3-propanediol (**2.39**) was monoprotected using the stable and commercially available 2-napthoyl chloride (**2.80**). To prevent protection of both alcohol functionalities, the starting diol was used in excess and thus the protecting group served as limiting reagent. In this way, and under nucleophilic catalysis, ester **2.81** was formed in 90% yield. The resulting alcohol could be directly allylated, using Krische's method, however the yield was only 44%. Therefore, an extra oxidation step was included to provide aldehyde **2.82**. The use of Swern conditions proved to be superior over other methods like Dess-Martin periodinane or TPAP-NMO in terms of yield (99% vs. 82% and 73%, respectively). Ir-catalyzed allylation from this oxidation level resulted in 68% of homoallylic alcohol **2.83**, which was 99% enantiomerically pure (e.e. 98%). Also, 25% of **2.84** could be isolated, emerging from migration of the protecting group to the secondary alcohol

and accounting for the lower yield. The absolute stereochemistry of the newly obtained alcohol was assigned by synthesizing the corresponding MTPA esters (**2.86** and **2.87**), measuring the ^{1}H-NMR spectra, subtracting the corresponding ppm values of both the (*R*)- and (*S*)-MTPA esters and applying the Mosher model (scheme 2.23 and figure 2.11). Vinylation of the homoallylic alcohol, using the Hg-catalyzed method, resulted in enol ether **2.85** in 82% yield.

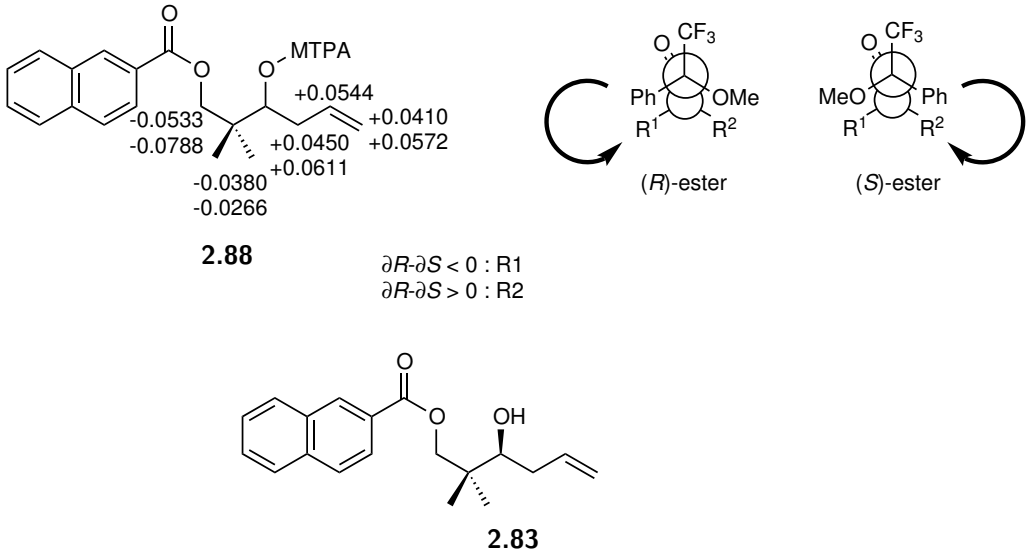


2.83

R' = Ph, R" = OMe : (*R*)-MTPA ester 89% **2.86**

R' = OMe, R" = Ph : (*S*)-MTPA ester 81% **2.87**

Scheme 2.23: Synthesis of the Mosher esters **2.86** and **2.87**



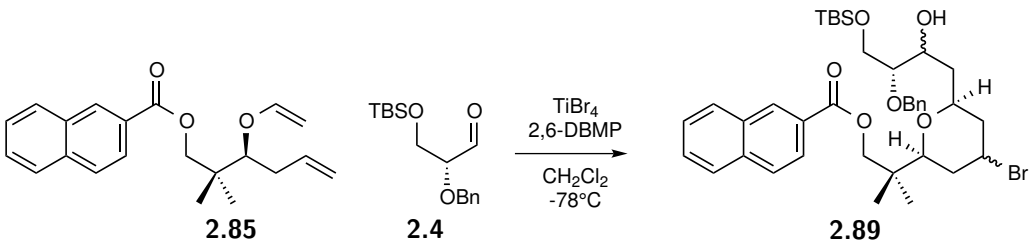
2.88

2.83

Figure 2.11: The Mosher model applied to **2.83**

2.7 The Mukaiyama aldol - Prins cyclization (II)

In a second attempt to form the THP ring, using the modified bisnucleophile **2.85**, the oxocarbenium ion indeed was trapped by the allyl group, resulting in the formation of THP ether **2.89** in 60%, be it as a mixture of four diastereomers (scheme 2.24). Also, the formation of a minor amount (7%) of **2.90** was observed, emerging from the 2-oxonia Cope rearrangement, which is a known side reaction during Prins cyclizations. The relative stereochemistry of this product was all-*cis*, however, the absolute stereochemistry was not determined.



Scheme 2.24: Second attempt on the Mukaiyama aldol - Prins cyclization

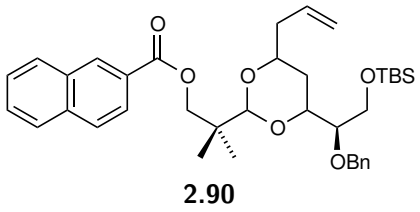
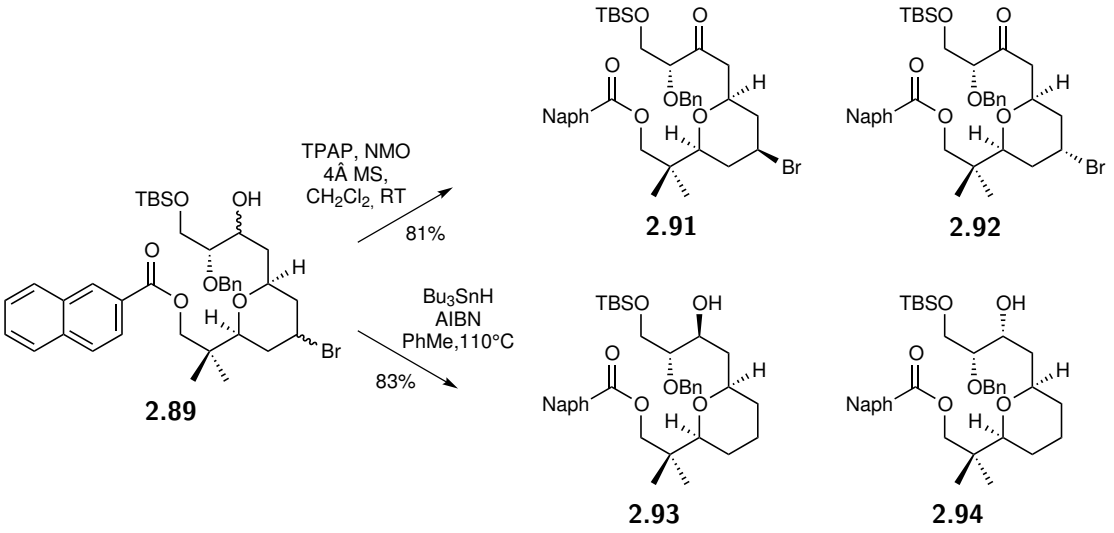


Figure 2.12: The 2-oxonia cope rearrangement product

These products, together with the excess of aldehyde, the bulky, non nucleophilic base and some side products, coming from deprotection of the TBS-ethers, resulted in a complex mixture, which was difficult to analyze. Several attempts to separate the diastereomers on normal or reversed phase LC failed (different gradients and different columns were tried). Moreover, only three peaks with the correct mass could be identified on reversed phase LC-MS. Therefore, what we

thought that was the mixture of diastereomers, was isolated (as a mixture) by flash column chromatography and submitted to chemical derivatization, in order to verify if it contained four diastereomers (Scheme 2.25).



Scheme 2.25: Chemical derivatization of the MAP diastereomers

A first part of the mixture was oxidized using the catalytic system of TPAP in combination with NMO. This resulted in a mixture of two diastereomers (together 81% yield), which could be separated by flash chromatography and -after NMR analysis- could be identified as the equatorial (**2.91**) and axial (**2.92**) bromide (1:1 ratio).

In a second part of the mixture, the bromine was radically reduced using Bu_3SnH and AIBN as initiator. This resulted also in a mixture of two diastereomers **2.93** and **2.94**, which now proved to be the epimeric alcohols (1:1). These results confirm that the original conditions for the MAP reaction indeed result in a mixture of 4 diastereomers.

In an attempt to improve the diastereomeric ratio, different conditions were tested (table 2.3).

In a standard experiment (entry 1, table 2.3), the Lewis acid is added to a mixture of enol ether and aldehyde at -78°C. Four diastereomers are formed in a

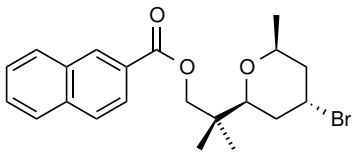
Entry	Lewis acid	remarks	observations
1	$TiBr_4$	fast addition	60% yield
2	$TiBr_4$	slow addition	78% yield
3	$TiBr_4$	precooled at -78°C	precipitation of $TiBr_4$
4	$TiBr_4$	change addition mode	TBS deprotection
5	$TiBr_4$:$Ti(iOPr)_4$ 9:1	-	ratio 1:1:1:1
6	$TiBr_4$:$Ti(iOPr)_4$ 1:1	-	more formation of **2.90**
7	$TiCl_4$	-	ratio 1:1:1:1
8	TMSBr	-	formation of **2.95**
9	TMSBr	2.5 eq. DBMP	formation of **2.95**
10	$Ti(iOPr)_4$	-	no reaction
11	$Ti(iOPr)_4$	quench with TMSBr	no reaction

Table 2.3: MAP test reactions

1:1:1:1 ratio, with a yield of 60%. A first observation (entry 2) was an improvement of the yield when adding the Lewis acid slowly. Unfortunately, the d.e. was unaffected. This improvement is mainly due to loss of the TBS group upon fast addition. As the catalyst is added as a solution in CH_2Cl_2, an attempt was made to precool this solution in order to gain better control of the temperature. Unfortunately, $TiBr_4$ precipitated at -78°C (entry 3). In order to gain better control of the stereoselectivity, the mode of addition was changed: first, the Lewis acid and aldehyde were combined, hence enabling chelation of the benzyl group, and afterwards the enol ether was added. This resulted mainly in deprotection of the TBS ether (entry 4). Different Lewis acids (blends) were used (entries 5-8), to investigate the steric and/or electronic effects thereof. Where the $TiBr_4$:$Ti(iOPr)_4$ 9:1 blend and $TiCl_4$ did not show an improvement in d.e., the $TiBr_4$:$Ti(iOPr)_4$ 1:1 blend showed a big increase in formation of the 2-oxonia Cope rearrangement product.

In all the above cases, and also in literature, the trapping nucleophile originated

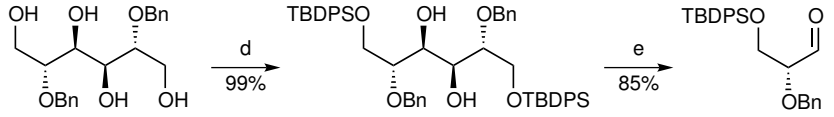
from the Lewis acid. Therefore, using a Lewis acid in catalytic amounts is not an option. Using a chiral BINOLTiBr$_2$ compound in stoichiometric amounts would be far too expensive. In order to develop a catalytic system, a bromide source should be added to the reaction mixture to trap the carbocation after Prins cyclisation. Therefore, first, the use of TMSBr as Lewis acid was tested. This resulted in formation of product **2.95** (figure 2.13), probably coming from enolization of the silyl activated aldehyde, hence producing HBr. In order to prevent this, the experiment was repeated with an excess of base, compared to the aldehyde (2.5 eq. base, 2 eq. aldehyde) (entry 9), unfortunately without improvement. Finally, pure Ti(iOPr)$_4$ was tested (entry 10), but did give no reaction, as judged from TLC. Also, after quenching with TMSBr (entry 11), no cyclization product was formed, and the starting enol ether was recuperated in 90% yield.



2.95

Figure 2.13: Reaction product when performing the reaction with TMSBr

The use of a more bulky silyl protecting group could possibly improve the stereoselectivity by increasing the sterical hindrance at the *Si* face, upon chelation with titanium. Therefore, a TBDPS ether was installed on the aldehyde (**2.96**), which was straightforward, starting from **2.37** (scheme 2.26)



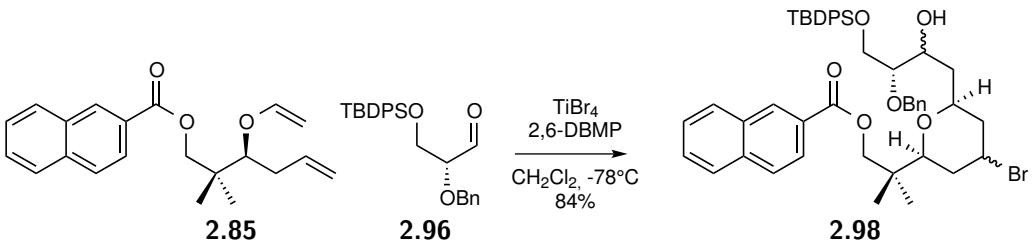
2.37 **2.97** **2.96**

a) TBDPSCl, imidazole, CH_2Cl_2, RT; e) $NaIO_4$, THF/H_2O 4/1, RT

Scheme 2.26: Synthesis of the TBDPS protected aldehyde **2.96**

Subjecting this aldehyde to the MAP cyclization conditions with enol ether

2.85 (scheme 2.27) resulted in 84% of the envisaged target material, unfortunately, again as a mixture of diastereomers in a 1:1 ratio. Also, 8% of the 2-oxonia Cope rearrangement product was isolated. No traces of silyl deprotected product were observed, which makes sense as a TBDPS ether is less acid sensitive than a TBS ether.

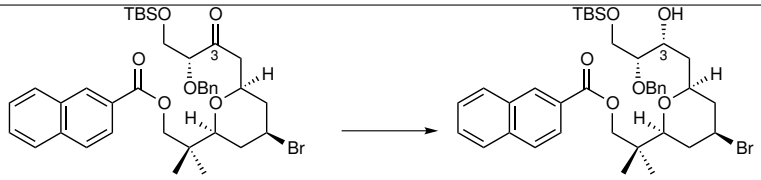


Scheme 2.27: MAP reaction with the TBDPS protected aldehyde **2.96**

2.8 Installing the correct stereochemistry

Earlier on, when analysing the diastereomeric mixture, it was shown that ketones **2.91** and **2.92** could be separated by column chromatography (scheme 2.25). Asymmetric reduction of these ketones would give access to the correct stereochemistry at C_3, thereby creating two sets of analogs: one with the axial bromide, and another one with the equatorial bromide. The results of the reduction are summarized in table 2.4.

First, the Corey-Itsuno reduction was tested. In this reaction, the ketone is reduced by borane in the presence of a chiral catalyst.[142,143] The catalyst, an oxazaborolidine, contains a methyl group on the endocyclic boron, and is derived from proline. Both enantiomers of this so-called CBS catalyst (named after Corey, Bakshi and Shibata) are commercially available as they are very air and moisture stable. The catalytic cycle, which also accounts for the stereoinduction, has been proposed to contain four important steps (scheme 2.28). First, the rapid and reversible coordination of BH_3 to the nitrogen of the catalyst (**2.100a**) activates the borane as a hydride donor and increases the Lewis acidity of the endocyclic

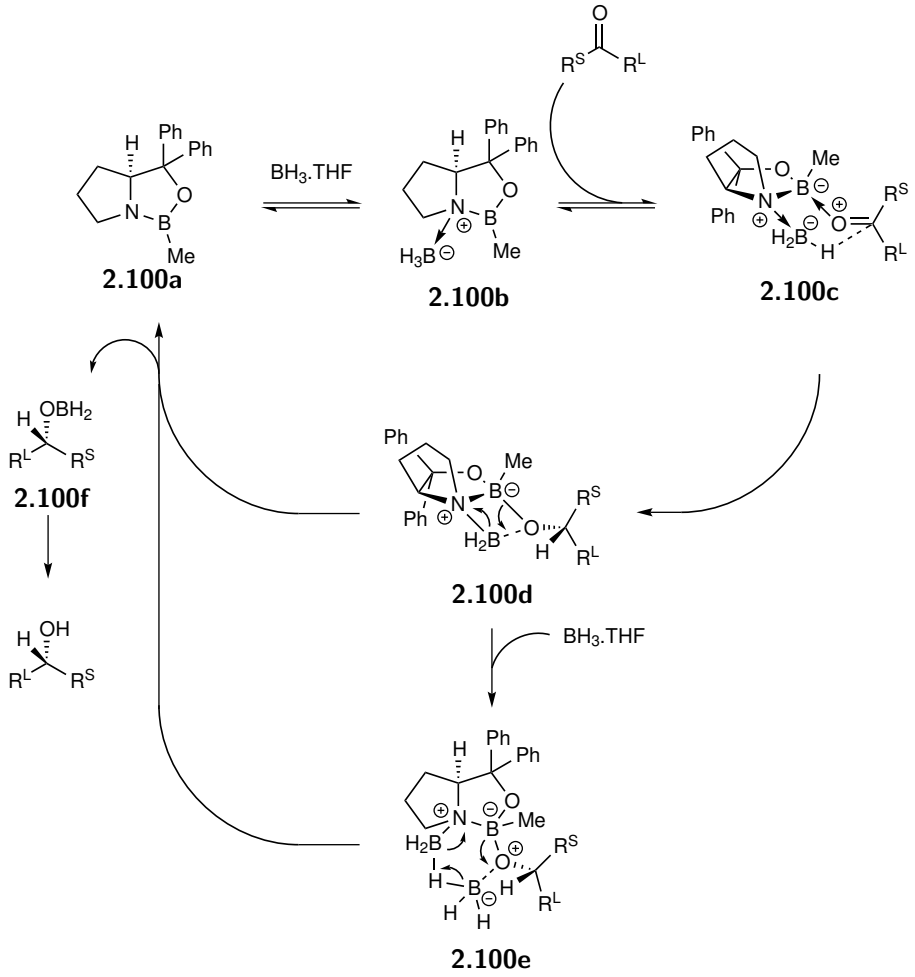


2.91 **2.99**

Entry	Reagent	Temperature (°C)	d.e. (%)
1	(*S*)-(-)-2-Me-CBS-oxazaborolidine	-30	54
2	(*S*)-(-)-2-Me-CBS-oxazaborolidine	-78	72
3	(*R*)-(+)-2-Me-CBS-oxazaborolidine	-78	60
4	L -selectride	-78	74
4	N -selectride	-78	74

Table 2.4: Asymmetric reduction of ketone **2.91**

boron atom of the catalyst (**2.100b**). ^{11}B-NMR and X-ray diffraction experiments proved the formation of this complex and also confirmed the structure to be *cis*-fused. Next, because of the rigid [3.3.0] ring system, the strongly Lewis acidic complex can only bind to the ketone, so that this ketone and the vicinal BH_3 group have a *cis*-*exo*-orientation and in such a way that the sterical interactions are minimized (**2.100c**). Therefore, the bigger the difference in size between the two R groups on the carbonyl, the better the stereoinduction. Moreover, binding in this way positions the electron deficient carbonyl carbon atom in alignment with the coordinated borane so it can undergo a face-selective intramolecular hydride transfer via a six-membered transition state. The regeneration of the catalyst and concomitant dissociation of the reduction product can occur in two ways. Either, the alkoxide ligand attached to the endocyclic boron of the complex reacts with the borane which is attached to the nitrogen *via* a cyclo-elimination (**2.100d**) or it reacts by addition of another molecule of borane to form a six-membered BH_3-bridged species (**2.100e**), which can in turn decompose to the catalyst and the borinate (**2.100f**).



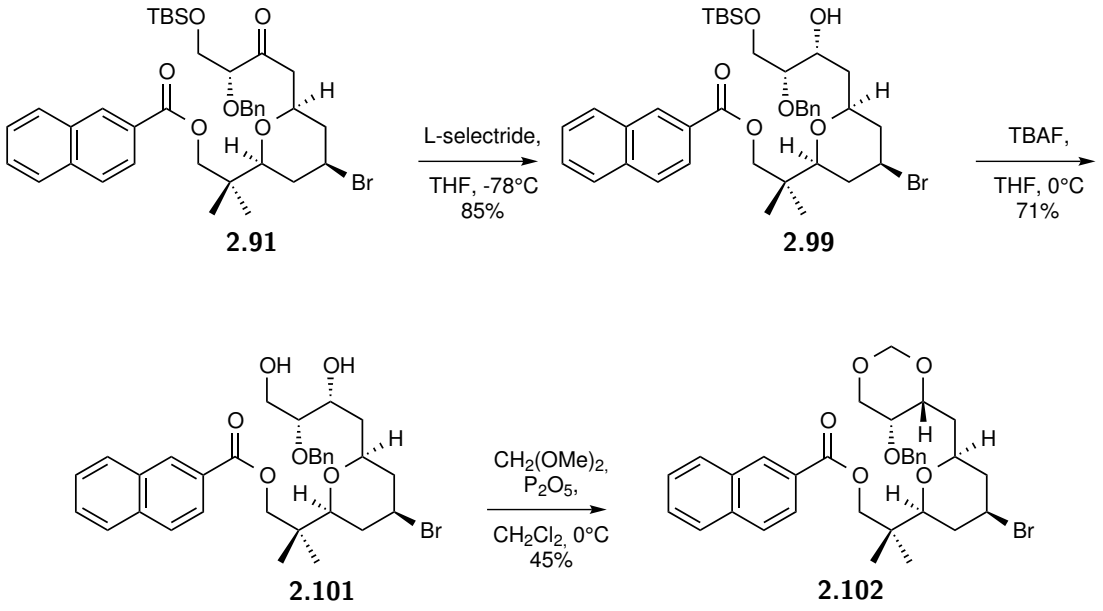
Scheme 2.28: Catalytic cylce for the CBS reduction

Assigning the methylene group next to the carbonyl in **2.91** (table 2.4) as the small group and the benzyloxy-methine as the large one, the use of the (*S*)-CBS catalyst should yield the correct stereochemistry. It can be seen clearly that a lower temperature is advantageous in terms of selectivity, going from a diastereomeric excess of 54% at -30°C (entry 1) to 72% at -78°C (entry 2). Unexpectedly, the use of the enantiomeric catalyst did not provide the opposite diastereomer as the major compound. Instead, there was a preference for the same diastereomer, with still an acceptable ratio of 80:20 at -78°C.

Another option was the use of stoichiometric amounts of steric organoborohydrides, especially tri-*sec*-butylborohydrides (selectrides). Both lithium (L) and sodium (N) selectride gave identical selectivity results (74% d.e.) as judged from LC-MS. After column chromatography, the diastereomeric ratio using L-selectride was increased to 93:7 (86% d.e.) with a total yield of 85%.

To prove the configuration at C_3 in **2.99**, we chose to make use of the stereocenter of the benzyloxy substituent at C_2, which is known, as it originates from the chiral pool. Therefore, the free rotation around the C_2-C_3 bond should be prevented. To do this, the TBS ether at C_1 was removed (**2.101**), and an acetal was formed between the resulting primary alcohol and the previously formed alcohol at C_3, thereby locking the conformation in a six-membered ring (scheme 2.29).

TBAF could deprotect the alcohol in a straightforward way, where the use of dimethoxymethane and P_2O_5 provided acetal **2.102** in a moderate yield of 45% (scheme 2.29).



Scheme 2.29: Synthesis of **2.102** to prove the absolute stereochemistry.

The approximate correlation between the dihedral angle formed by two coupled

protons and the observed vicinal coupling constant (^{3}J) in the NMR spectrum is described by the Karplus equation.[144–146] In the original equation, $^3J(\phi) = Acos^2\phi + Bcos\phi + C$, ϕ is the dihedral angle, and A, B, and C are empirically derived parameters. However, there are other structural parameters that influence the scalar coupling, for instance the electronegativity of attached substituents or the relative disposition between them. Therefore, Altona *et al.* came up with a a more complex equation, taken into account these effects. The actual equation is rather complex and requires the electronegativities of all substituents to be entered.[147]

Using the program Mspin,[148] we could come up with a Karplus curve for **2.102**, as depicted in figure 2.14.

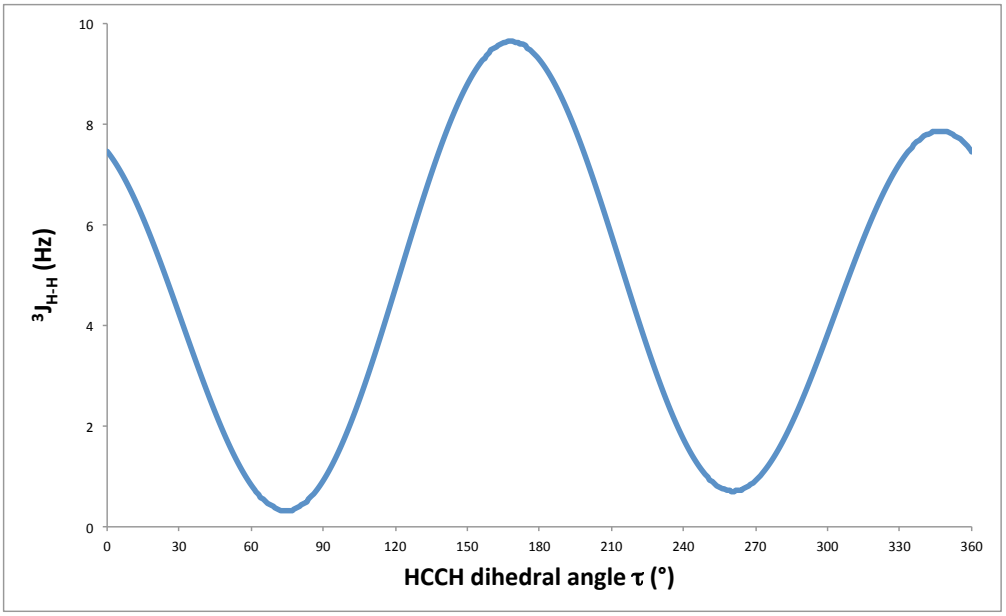


Figure 2.14: The Karplus curve for vicinal protons at C_2-C_3 in **2.102**

Assuming the 1,3-dioxane **2.102** adopts a chair conformation, and the C_3 center possesses the correct (*R*)-stereochemistry, there are two possible conformers: one where the benzyloxy group occupies an equatorial postion and the methylene-linked tetrahydropyran the axial position, or *vice versa* (figure 2.15, left). In both

cases, there will be a small dihedral angle between the vicinal protons at C_2 and C_3, hence a small scalar coupling is expected.

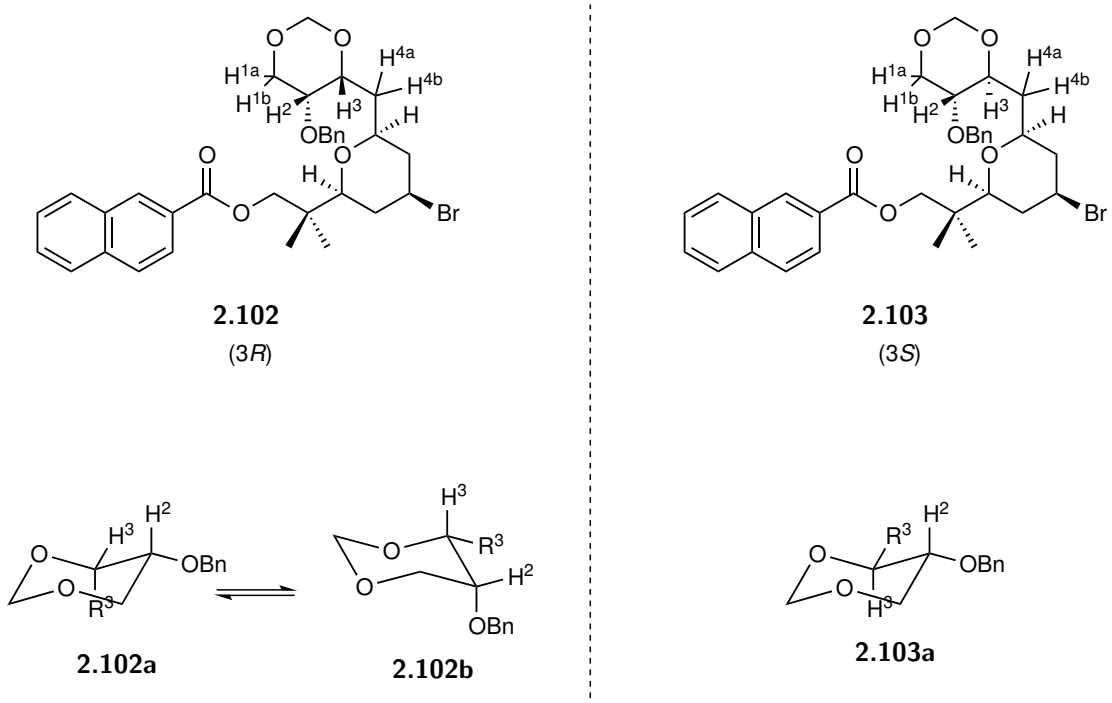


Figure 2.15: Possible conformers for **2.102** (left) or its unwanted diasteromer **2.103** (right)

In the other case, when the C_3 center possesses the unwanted (S)-stereochemistry, only one conformer will prevail, where both substituents of the dioxane ring adopt an equatorial position (figure 2.15, right). In this case, the dihedral angle between vicinal protons on C_2 and C_3 will be approximately 180°, corresponding to a big scalar coupling.

When looking at the ^{1}H NMR spectrum of **2.102**, proton H^3 has three different coupling partners, resulting in a ddd signal with coupling constants 9.9, 5.1 and 1.7 Hz. The largest of these couplings constants (9.9 and 5.1 Hz) originate from the adjacent methylene protons H^{4a} and H^{4b}. The smallest one should then evidently originate from coupling with H^2. It is however hard to isolate this coupling constant when looking at this proton H^2 in the spectrum due to some overlap.

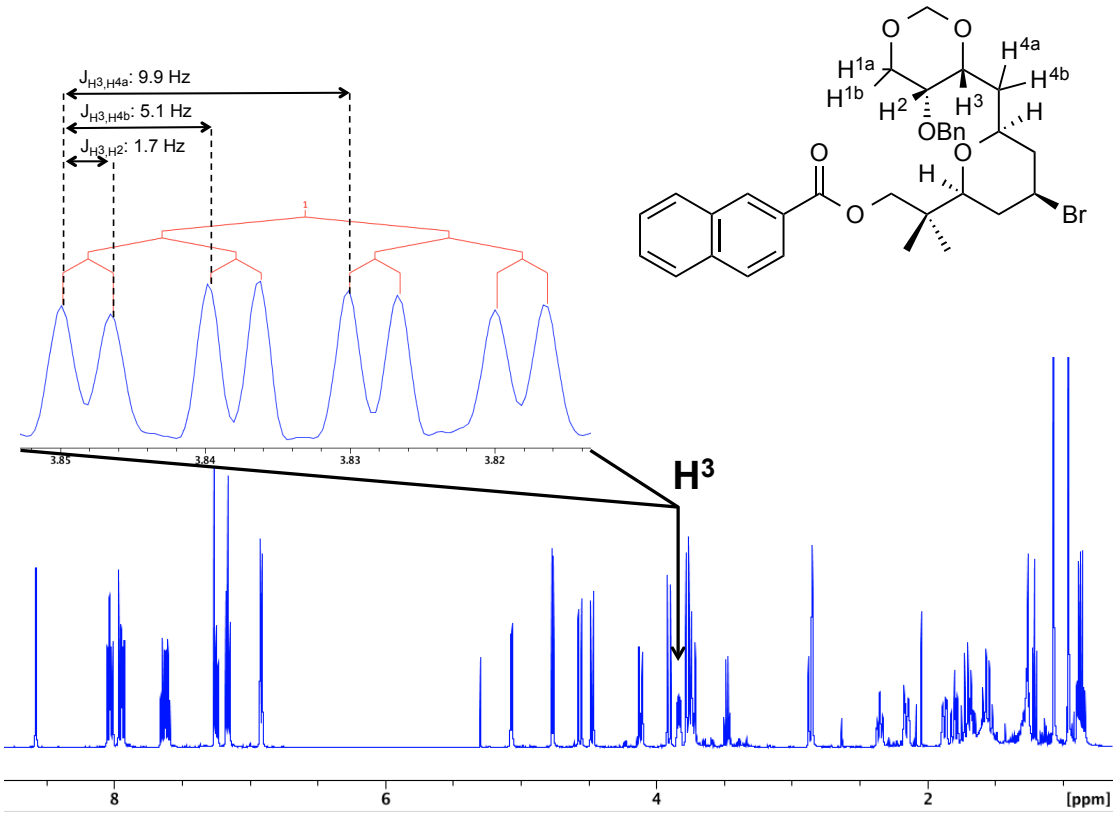


Figure 2.16: ^{1}H NMR spectrum of **2.102** in $CDCl_3$ (500 MHz)

The coupling constant of 1.7 Hz for J_{H_2,H_3}correlates in the Karplus curve with a small dihedral angle, which corresponds with conformers **2.102a** or **2.102b**. This is a first clue that the obtained stereochemistry is the desired one. To be completely sure, however, the undesired diastereomer should be synthesized, and the NMR spectrum should be compared with that of the desired one.

Unfortunately, at this point in time, the priorities of our research group shifted towards other analogs. Therefore, I could not pursue the completion of the THP analog. Overall, the Mukaiyama aldol - Prins approach proved powerful for the generation of the tetrahydropyranyl ring, be it without the desired control of stereochemistry. To avoid the encountered problems to introduce the stereochemistry, it might be better to pursue an alternative synthesis (see future perspectives).

3

Phenyl analogs

During the second year of my PhD, a simplified peloruside analog that was synthesized before, was biologically tested *in vitro* and showed promising activity. Therefore, I was assigned to re-evaluate the synthesis route of this phenyl analog and design (a route towards) new analogs, based on the simplified ring system. In this chapter, the results concerning these topics are discussed.

3.1 Introduction

3.1.1 Pelofen B

During a previous PhD, pelofen B (**3.1**) was synthesized: an analog of peloruside B where the pyranose ring has been replaced by a phenyl ring.[149] The total number of stereocenters was thus reduced from 10 to 6, thereby diminishing the synthetic complexity. As in peloruside B, the alcohols at C_2 and C_3 are not differentiated and the activity stays the same, **3.1** is an analog of peloruside B, thereby further reducing the molecular complexity. The compound was tested for its biological activity in collaboration with prof. Bracke (laboratorium for experimental cancer research), which led to some promising results (table 3.1).

On a weight per volume basis, pelofen showed, in a qualitative test, an equal potency as paclitaxel in its ability to disturb the cytoplasmatic microtubule complex in PTK-2 cells. This should be considered with care, as pelofen has a molecular weight of 464 g/mol, whereas paclitaxel weighs almost twice as much (854 g/mol). However, the lower molecular weight could also be advantageous, as it is associated with better cell penetration through the membrane and reduced aspecifc cytotoxicity.

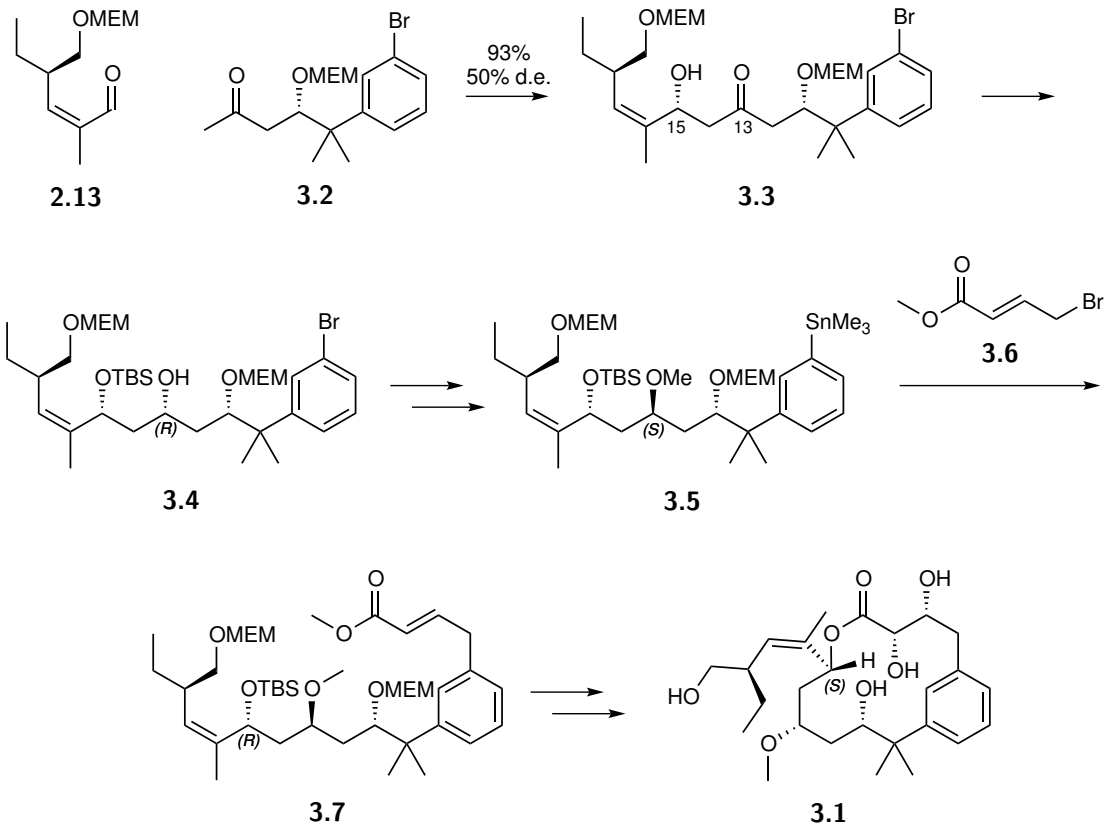
Treatment	Concentration	State of cytoplasmatic MT-complex after		
	(μg/ml)	1h	5h	24h
DMSO	-	normal	normal	normal
paclitaxel	0.1	normal	disturbed	disturbed
	1.0	disturbed	disturbed	disturbed
pelofen	0.1	disturbed	disturbed	disturbed
	1.0	disturbed	disturbed	disturbed

Table 3.1: Results of the first experiments on the *in vitro* activity of pelofen, compared to paclitaxel.

Therefore, it was decided to further investigate the potential of this molecule.

In order to do this, the amount of pelofen had to be scaled up, and new analogs had to be developed in order to investigate the SAR of pelofen and, indirectly of peloruside. Most of the results of this thesis are part of a patent, which was filed in 2015.[150]

In the original synthesis route (scheme 3.1), the key coupling steps are an asymmetric aldol reaction between aldehyde **2.13** and methyl ketone **3.2**, and a Stille reaction for the introduction of the C_1-C_3-unit. Whereas for the introduction of the stereochemistry, an asymmetric reduction and a Sharpless asymmetric dihydroxylation were used. After installation of the correct stereochemistry, a standard ring-closing macrolactonization resulted in formation of the 16-membered macrolactone, which, after deprotection, yielded the simplified peloruside B analog **3.1**.



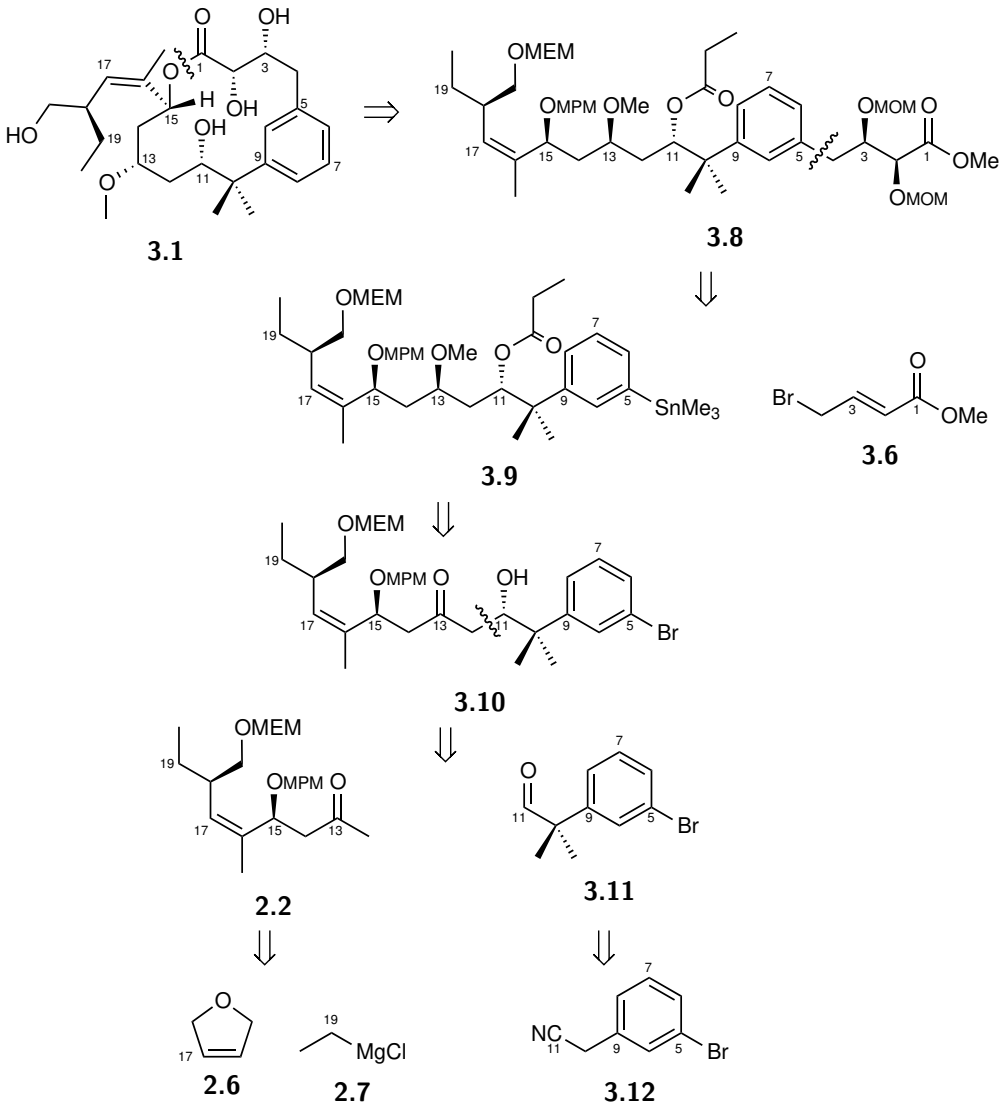
Scheme 3.1: Original synthesis route towards pelofen B (**3.1**)

The original synthesis however, contained some flaws. Firstly, the aldol reaction between fragment **2.13** and methyl ketone **3.2** induced the inverse stereochemistry at C_{15} (**3.3**). Secondly, this was only discovered later, so the asymmetric 1,3-*syn* reduction originally also installed the inverse stereochemistry at C_{13} (**3.4**). The wrong stereocenters could be corrected in three extra steps: the correct stereochemistry at C_{13} was inverted under Mitsunobu conditions (**3.4** to **3.5**), whereas the stereochemistry at C_{15} could be inverted using an oxidation - CBS reduction protocol (**3.7** to **3.1**). Thirdly, the final steps in the synthesis of **3.1**, the macrolactonization and the final deprotection, were low yielding (36% and 40%, respectively), causing a significant drop in overall yield. Therefore, a new synthesis was developed, avoiding the previously observed obstacles (scheme 3.2).

3.1.2 New synthesis of pelofen B

The newly developed retrosynthetic analysis (scheme 3.2) starts with the disconnection at the lactone moiety, in the forward route corresponding again to a macrolactonization. The second disconnection is also identical to the original route, were a Stille reaction between phenyl fragment **3.9** and γ-bromocrotonate **3.6** should assure the coupling. The biggest difference in the new synthesis route lies in the construction of fragment **3.9**. Whereas in the original route, the stereochemistry at C_{11} is already established before, and the stereochemistry at C_{15} is the result of the aldol coupling, in the new route, it is the other way around. Thus, in the new synthesis of **3.1**, fragment **3.9** is constructed via aldol product **3.10**, which is the result of the coupling between a methyl ketone **2.2**, where the stereochemistry at C_{15} is already established, and a prochiral aldehyde **3.11**. In this way, the correct stereochemistry at C_{11} is directly installed, and the synthesis becomes shorter. Next, an Evans-Tishchenko reduction would directly install the correct stereochemistry at C_{13}, and also differentiate between the alcohols at C_{11} and C_{13} by protecting the former as an ester. We envisaged the simultaneous deprotection of this ester with the methyl ester when setting free the hydroxy acid needed for macrolactonization. In this way, the final deprotection would also become easier,

as it was especially the sterically hindered MEM ether at C_{11} which required the harsh conditions in the original synthesis. Aldehyde **3.11** can be constructed in only two steps, starting from 2-bromophenyl acetonitrile (**3.12**), which is commercially available. The synthesis of methyl ketone **2.2** starts from 2,3-dihydrofuran (**2.6**) and ethylmagnesium bromide (**2.7**) and was described in chapter 2 (scheme 2.3).

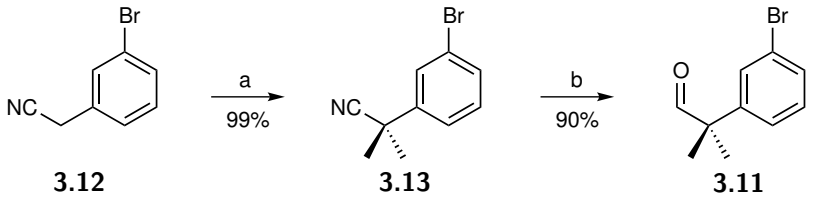


Scheme 3.2: New retrosynthetic analysis of pelofen B (**3.1**)

3.2 Results and discussion

3.2.1 Construction of the C_5-C_{20} fragment 3.9

Aldehyde **3.11** is prepared, according to a known procedure, starting from the commercial 2-bromophenyl acetonitrile **3.12** in two steps.[149,151] First, double methylation of the benzylic postition delivers the *gem*-disubstituted nitrile **3.13** in 99% yield. Subsequent reduction of this nitrile and acidic workup yields aldehyde **3.11** in 90% (scheme 3.3).

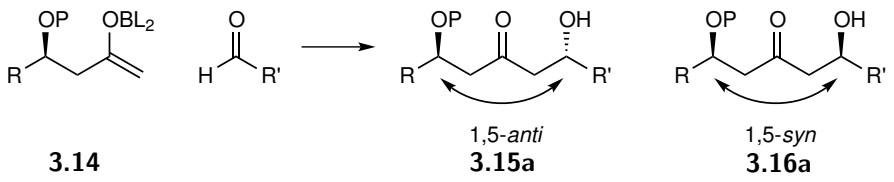


a) KO*t*Bu, MeI, THF, -40°C; b) [i] DIBAH, PhMe, -78°C, [ii] 6M aq. HCl, RT

Scheme 3.3: Construction of the C_5-C_{11} aldehyde **3.11**

The key steps for the completion of the C_5-C_{20} fragment include a 1,5-*anti* aldol addition, an Evans-Tishchenko reduction and a Stille Coupling to the stannane (*vide infra*).

The 1,5-*anti* aldol addition



Scheme 3.4: Remote asymmetric induction in the boron aldol reaction of a β-alkoxy methyl ketone

The first observation of remote 1,5-*anti* induction in the aldol reaction of methyl ketone-derived enolborinates was done by Masamune and coworkers in 1989 in their work towards the synthesis of the C_1-C_{16} fragment of bryostatin 1.[152] Although the selectivity was low (1,5-*anti* vs 1,5-*syn* 2:1), this represented evidence for remote induction to stimulate further research. Paterson[153] and Evans[154] simultaneously came up with empirical examples of remote 1,5-*anti* induction with very good selectivity. They both concluded that the nature of the protecting group on the β-oxygen (**3.14** in scheme 3.4) is critical in determining the level of stereoinduction: benzylic ethers and acetals gave good 1,5-*anti*-induction (**3.15a**), whereas the use of a silyl ether gave an alteration in diastereoselection (**3.15b**).

The applicability of this type of aldol reaction was demonstrated in the synthesis of a variety of natural products possessing 1,3-polyol motifs,[155] among which peloruside.[156]

The origin of the selectivity was first thought to arise from a π-stacking interaction between benzylic protecting groups and the boron enolate in the cyclic transition state. However, this could not explain the obtained high levels of induction with β-alkoxy substituents like OMe, or cyclic ethers like tetrahydropyranyl rings.[157]

Early computational studies by Houk[158,159] and Bernardi[160] had shown that chair-like and boat-like transition states in boron-mediated aldol reactions of methyl ketones are relatively close in energy. Further studies by Paton and Goodman[161,162] confirmed this and proposed four possible transition states, dependent on the orientation of the extra-annular β-alkoxy substituent (figure 3.1). This substituent can be oriented away from the cyclic transition structure (boat-out **3.17b**, chair-out **3.18b**) or can be oriented back toward the cyclic core (boat-in **3.17a**, chair-in **3.18a**).

The first simulations on a simple, non-chiral boron-enolate (figure 3.1) revealed that the boat conformation where the alkoxy side chain is folded toward the approaching aldehyde and the forming C-C bond (boat-in, **3.17a**) is preferred. On steric grounds, this is counter-intuitive, but it appeared that the distance be-

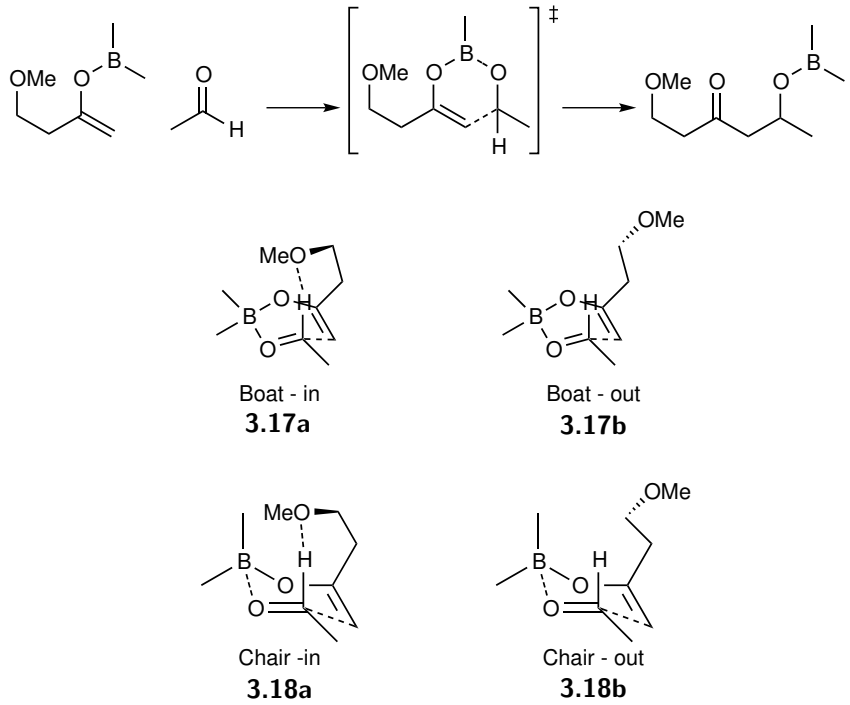


Figure 3.1: Competing transition structures for the boron aldol reaction of an achiral β-methoxy methyl ketone with ethanal according to Goodman[161]

tween the β-oxygen and the formyl hydrogen is rather short, suggesting a favorable formyl-hydrogen bond. In the corresponding chair conformation (chair-in), the C-H–O distance is somewhat bigger, therefore resulting in less stabilization. Moreover, when achieving a close C-H–O contact, the β-carbon eclipses the enolate double bond, resulting in 1,3-allylic strain.

As the boat-like transition structures are the most favorable ones, for the calculations on more advanced structures, where the β-center is chiral, only these were considered. Also for these systems, because of the formyl hydrogen bond, a boat-shaped structure where the alkoxy group is folded back inside is favored. However, because of the chirality of the β-center, discrimination between two different transition states is now possible (figure 3.2): 1,5-*anti* **3.19** and 1,5-*syn* **3.20**. Here, the 1,5-*anti* transition structure **3.19** is favored, because it lacks any steric interactions between the β-alkyl group and one of the ligands on boron, an interaction

which is notably present in the 1,5-*syn* transition structure **3.20**.

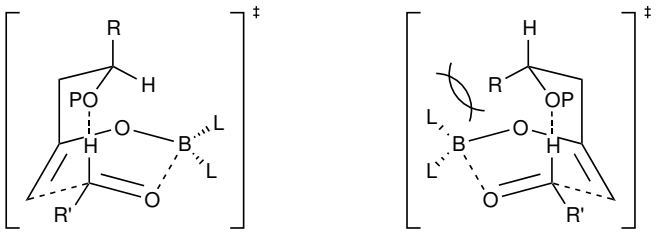


Figure 3.2: Diastereomeric 1,5-*anti* and 1,5-*syn* transition structures according to Goodman[161]

These postulations resulted in a model transition state where the formyl hydrogen is part of a seven-membered ring with the enolate and the forming C-C bond. This model is in agreement with the experimental results: methyl ethers, benzyl ethers and acetals are capable of forming the hydrogen bond and result in 1,5-*anti* induction. Silyl ethers on the other hand have no preference for an internal hydrogen bond because of the lower electron density of the oxygen and the bigger steric impediment, so there will be less selectivity. Also the fact that the selectivity is lower in more polar solvents, is in agreement with this model as more polar solvents will attenuate the electrostatic interactions between the formyl hydrogen and the alkoxy oxygen.

Dias and coworkers expanded the model proposed by Goodman, as they observed that this model is not in agreement with some experimental results (figure 3.3).[163] Thus, they assumed the Goodman-model is only applicable for methyl ketones with small and medium β-alkyl substituents and they proposed a complementary model of induction that includes both the volume effect of the β-substituent as that of the protecting group at the β-oxygen. According to the improved model, in case of a bulky β-alkyl group (t-Bu, Ph_3C-) and a protecting group of intermediate size (P=Bn, MPM, TBS), the transition structures were the β-alkoxy substituent is pointing towards the cyclic core and thus capable of forming a hydrogen bond, now are energetically unfavorable, because of the in-

creased steric repulsions (**3.21** for the 1,5-*anti* transition structure, **3.22** for the 1,5-*syn* transition state). Therefore, in this particular case, the *out*-transition states should be considered, where the bulky β-substituent points away from the ring and the ligands on boron as far as possible. Discrimination between 1,5-*anti* and 1,5-*syn* is now a consequence of the position of the -OP group. In the 1,5-out *anti* transition structure (**3.23**) the oxygen of this -OP is in close proximity with the oxygen of the enolate (electronic repulsion) and the protecting group clashes with a ligand on boron (steric repulsion). Therefore it is higher in energy. The 1,5-out *syn* transition structure (**3.24**) on the other hand, positions the -OP bond opposite of the C-O enolate bond, therefore lowering both electronic and steric repulsions. According to Dias' proposed model, in case of a large alkyl group and an intermediate protecting group, the 1,5-*syn* adduct will thus prevail. This selectivity will be lost again when a larger protecting group is used, thereby introducing new repulsive interactions. This is in perfect agreement with the observed experimental results.[163,164]

The previously described model(s) explain why in the original synthesis of pelofen, the 1,5-*syn* aldol product was obtained. The methyl ketone contained a protecting group with an intermediate size (MEM-ether), and a bulky β-alkyl substituent. Therefore, the model of Dias should be applied (**3.24**), which accounts for the observed *syn*-selectivity. Anticipating this problem, we chose to make use of achiral aldehyde **3.11** and couple it with methyl ketone **2.2** (scheme 3.5), which possesses a relatively small sp^2-hybridized β-alkyl substituent and an intermediate-sized protecting MPM-group. Application of the Goodman-model, results in the prevalence of the 1,5-in-*anti* transition structure (**3.19**) and thus the envisaged selectivity.

Generation of the boron enolate is achieved by adding chlorodicyclohexylborane and triethylamine to methyl ketone **2.2**. Addition of aldehyde **3.11** at -78°C results in the formation of **3.10** as a single diastereomer in 88% yield. At this stage, the absolute stereochemistry was indicated by Mosher ester analysis.

Both (*R*)- and (*S*)- MTPA esters were prepared in a modest yield (54% and 38%, respectively) and had to be purified using preparative HPLC (scheme 3.6).

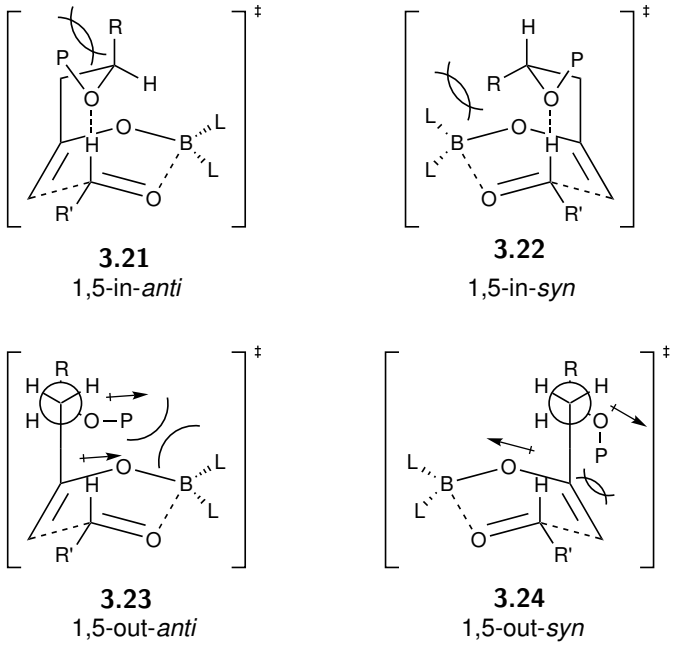
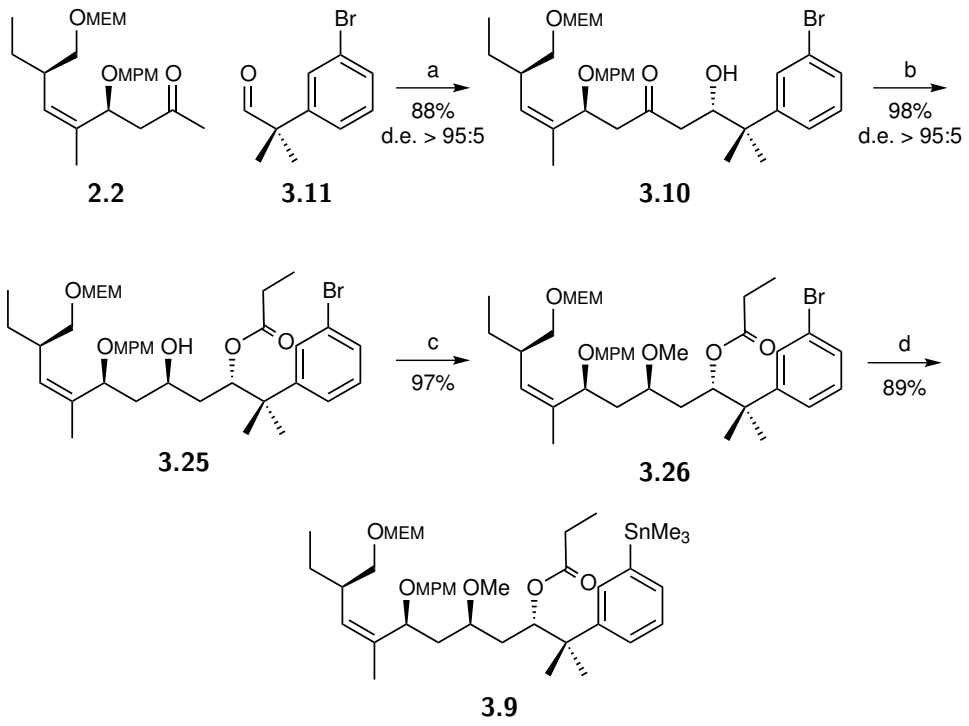


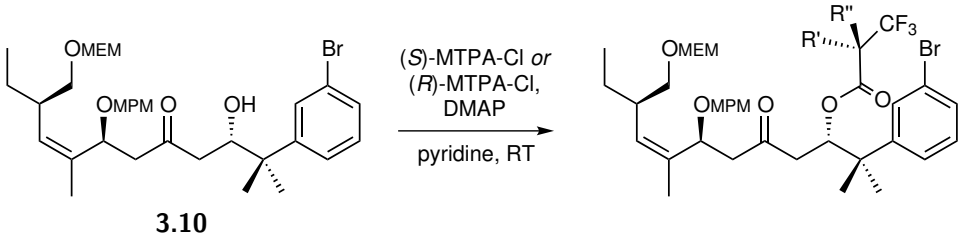
Figure 3.3: Diastereomeric 1,5-*anti* and 1,5-*syn* transition structures according to Dias[163]

Not all protons could be assigned in the ^{1}H-NMR spectrum, as there were overlapping signals, especially in the aromatic region. Therefore, only one proton signal of the phenyl ring was available to apply the model (figure 3.4). The difference in chemical shift between the (*R*)- and (*S*)- ester is in agreement with the proposed stereochemistry at C_{11}. However, as the available set of data points on the right hand side of the molecule was limited, the stereochemistry was also verified, relative to the stereochemistry at C_{15}. This could only be achieved after reduction of the ketone.



a) [i] $(Cy)_2BCl$, NEt_3, Et_2O, -78°C; [ii] MeOH, pH 7 buffer, H_2O_2, RT; b) EtCHO, SmI_2, THF, -20°C; c) Me_3OBF_4, 1,8-bis(dimethylamino)naphtalene, CH_2Cl_2, RT; d) $Me_3SnSnMe_3$, $Pd(PPh_3)_4$, PPh_3, PhMe, 70°C

Scheme 3.5: Construction of the C_5-C_{20} fragment **3.27**



Scheme 3.6: Synthesis of the Mosher esters **3.28** and **3.29**

Thus, the resulting β-hydroxy ketone was stereoselectively reduced by means of

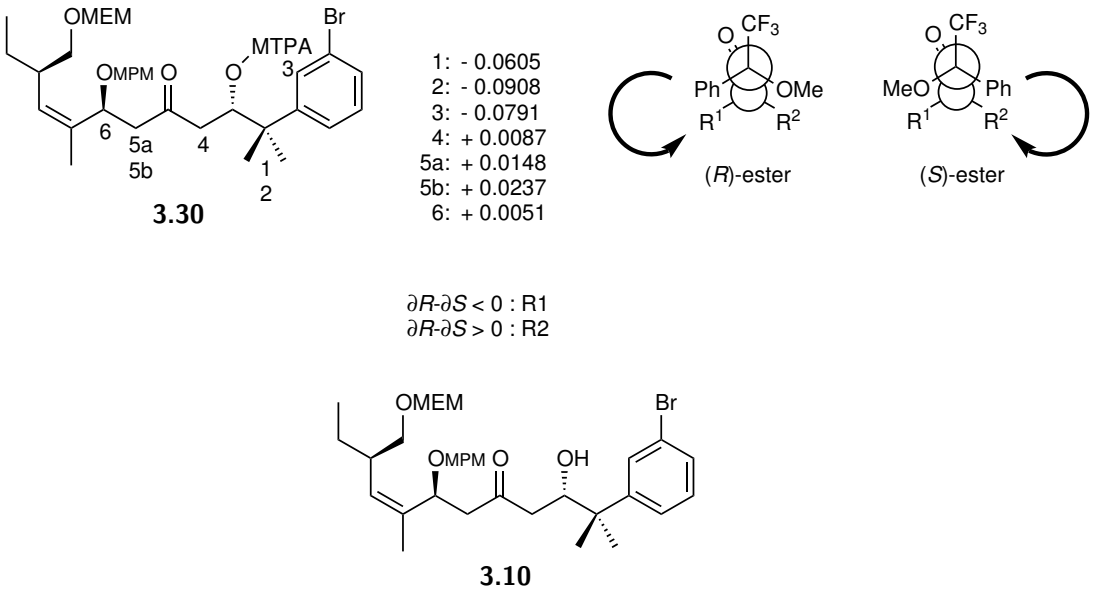
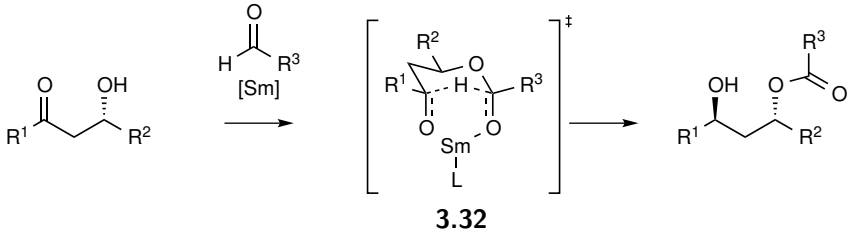


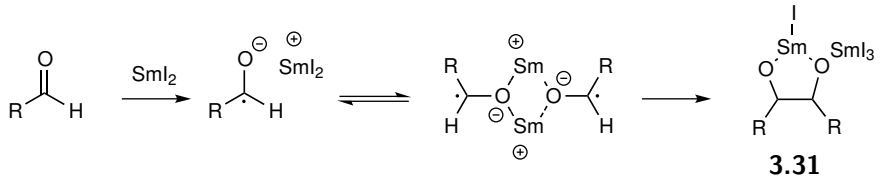
Figure 3.4: The Mosher model applied to **3.10**

a SmI_2-catalyzed intramolecular Evans-Tishchenko reduction (scheme 3.5).[165,166] The Tishchenko reduction is the Lewis acid mediated condensation of two equivalents of an aldehyde to form an ester. The variant, reported by Evans in 1990 entails the Lewis acid catalyzed condensation of a β-hydroxy ketone with an aldehyde to form a 1,3-*anti* diol monoester (scheme 3.7). It has been suggested that the catalytic species is samarium(III) pinacolate **3.31**, generated from SmI_2 and the aldehyde (scheme 3.8) through a pinacol reduction. This explains the change of colour from deep blue to yellow upon addition of this aldehyde.



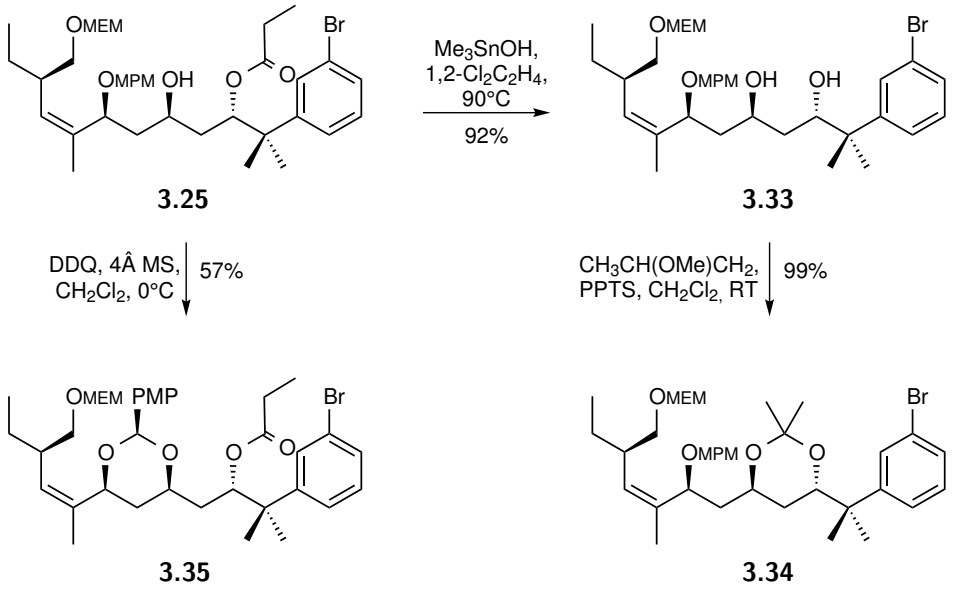
Scheme 3.7: The Evans-Tishchenko reduction

The proposed mechanism for this reaction involves Lewis acid catalyzed hemi-



Scheme 3.8: Generation of a catalytically active samarium(III) pinacolate

acetal formation, followed by intramolecular hydride transfer to the newly formed carbinol center, *via* a 6,6-chair type transition state (**3.32** in scheme 3.7). The stereoselectivity itself may be attributed to the coordination of Sm to both carbonyl and hemiacetal oxygens.



Scheme 3.9: Proof of the relative stereochemistry (I)

To prove the *anti*- relationship between the alcohol at C_{11} and the one on C_{13}, the propionate ester was removed, and an acetonide (**3.34**) was installed (scheme 3.9). From inspection of the ^{13}C chemical shifts of this acetonide, the relative configuration can be assigned.[167,168] This is based on the difference in conformation between a *cis*-1,3- and an *trans*-1,3-diol acetonide. Most 1,3-dioxanes, including *cis*-1,3-acetonides exist in a chair conformation, as depicted in figure 3.5. *Trans*-

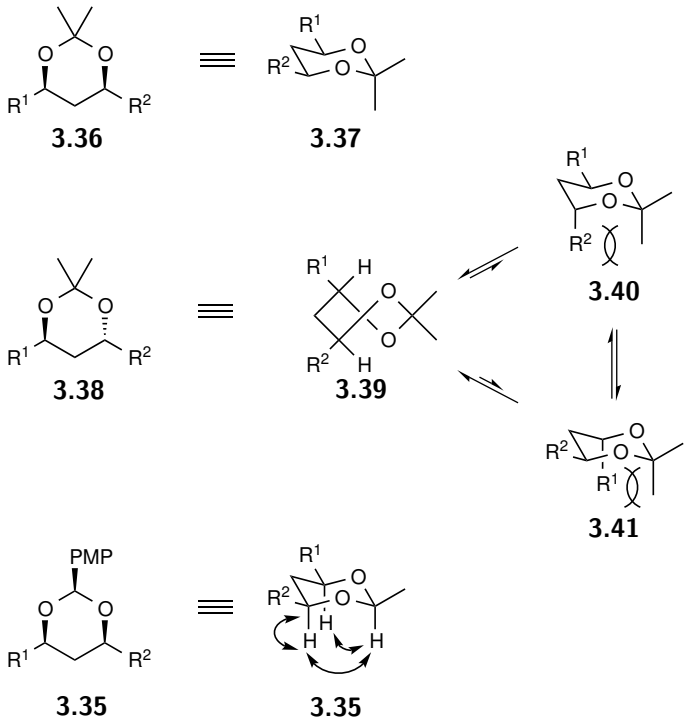


Figure 3.5: Proof of the relative stereochemistry (II)

1,3-acetonides are the exception, resulting from a severe 1,3-*syn*-diaxial interaction between an R group and one of the methyl groups of the acetonide in the chair conformation. Therefore, the *trans*-1,3-acetonide will adopt a twist-boat conformation, where the dioxane is nearly C_2-symmetrical (not taking into account the difference between R^1 and R^2). As a result, the chemical shift of the methyls of the acetonide will be nearly identical. On the other hand, when a 1,3-dioxane adopts a chair conformation, as in the case of a *cis*-1,3-acetonide, the methyl groups are diastereotopic, and therefore have a different chemical shift. From extensive literature search by Rychnovsky[169] the chemical shift of the methyls of a *trans*-1,3-acetonide in the ^{13}C spectrum on average is 24.6 ppm, whereas in case of a *cis*-1,3-acetonide, one methyl group has a chemical shift of around 30.0 ppm, and the other around 19.6 ppm. Evans had also pointed out earlier that the chemical shift of the central acetal carbon correlates well with the *cis* and *trans* conformation, the former having an average chemical shift of 98.5 ppm, while the latter has

an average shift of 100.6 ppm.[170]

In our case, the ^{13}C chemical shift of the two methyls are 25.0 and 24.4 ppm, respectively. Also, the central quaternary carbon has a chemical shift of 100.5 ppm. All these results confirm the *anti* conformation between the two hydroxyls.

To have a solid proof of the 1,5-*anti* induction during the aldol reaction, the relation between the stereocenter at C_{13} and the previously determined one at C_{15} should be established. Therefore, the *p*-methoxyphenyl acetal **3.35** was formed (scheme 3.9). This could be achieved under anhydrous, oxidative conditions, using DDQ. NOESY-analysis of the formed, chair-like 1,3-dioxane shows crosspeaks between the axial protons of acetal **3.35**, thus confirming the 1,3-*cis*-relationship (figures 3.5 and 3.6).

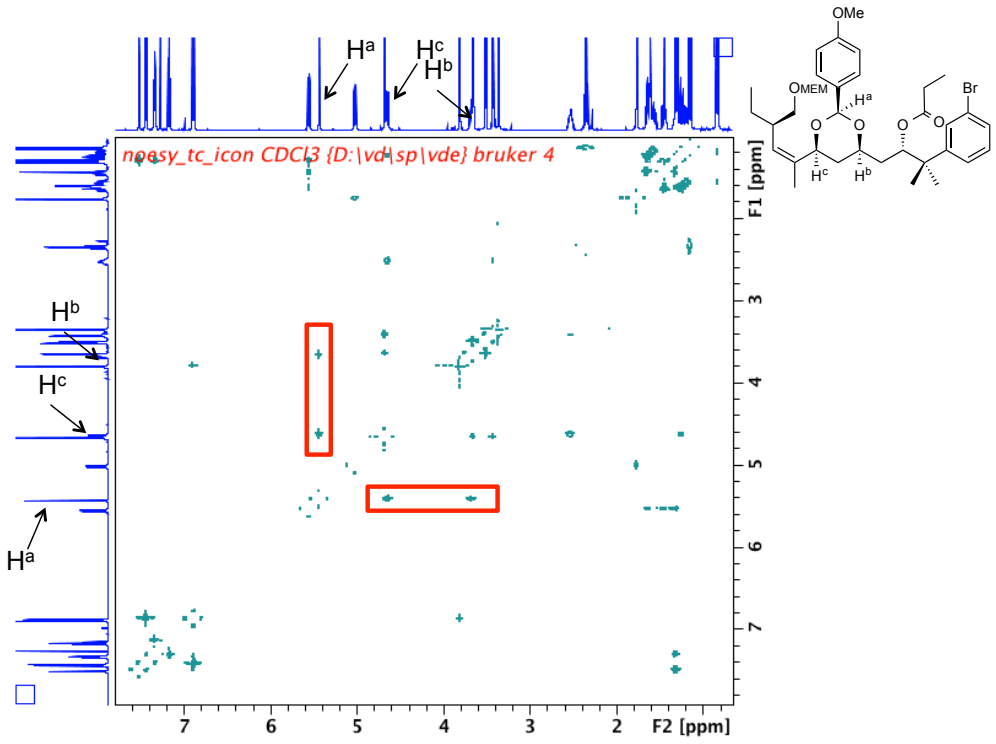
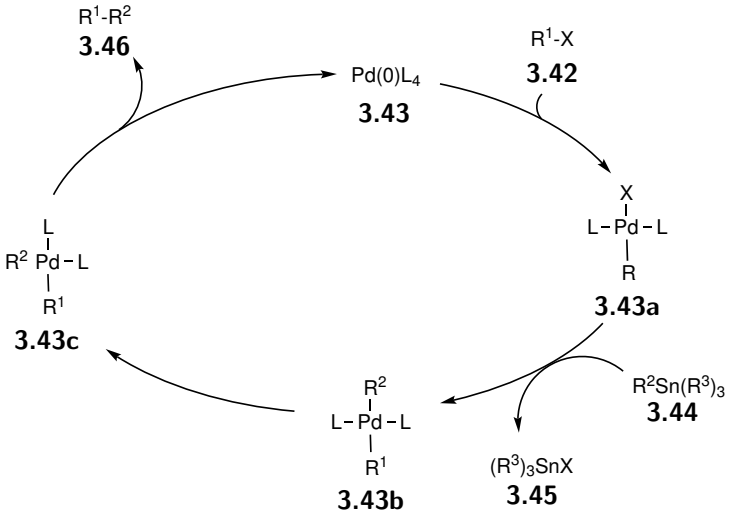


Figure 3.6: NOESY spectrum of **3.35** in $CDCl_3$

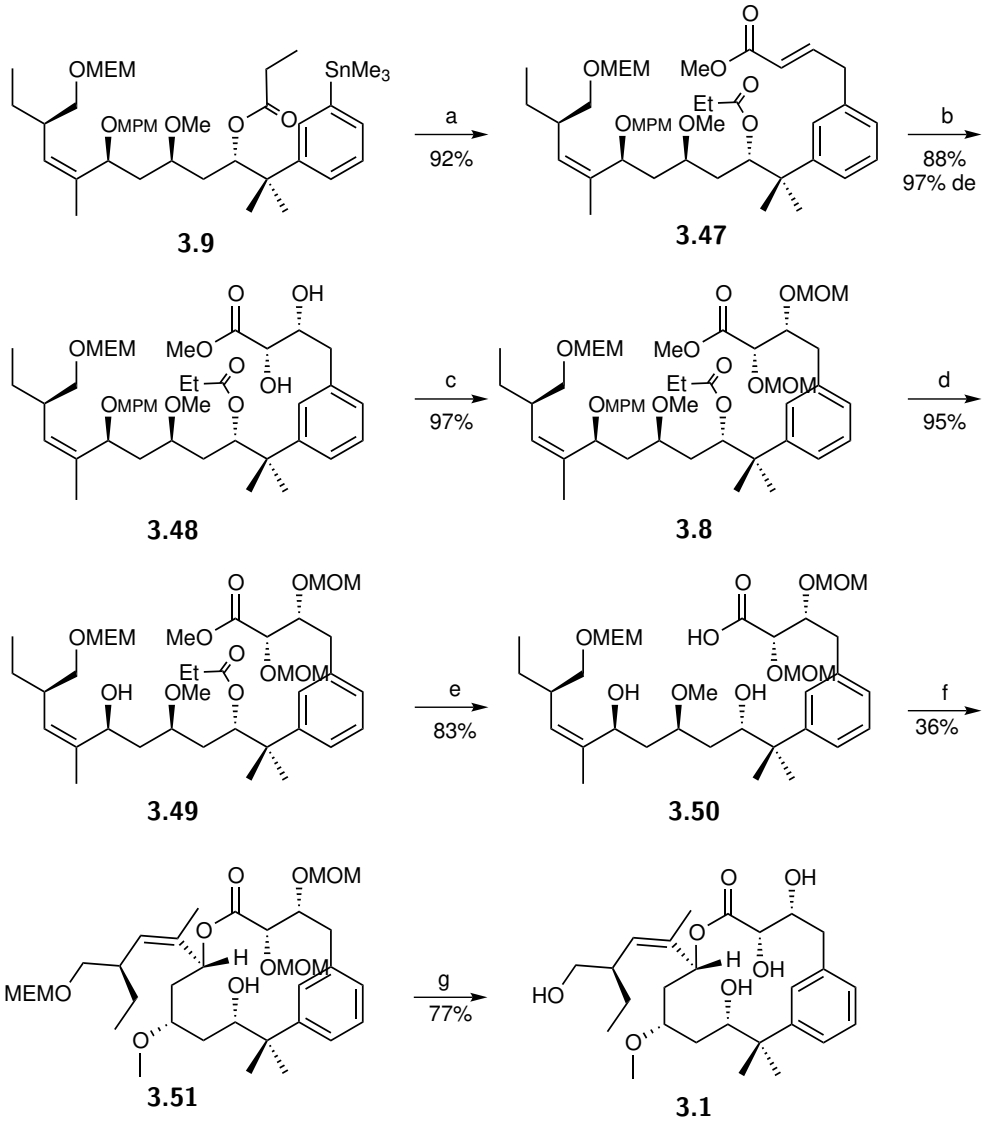
Since the efforts to prove the correct chemistry all pointed in the good direction,

the synthesis of the C_5-C_{20} fragment (**3.9**) was continued (scheme 3.5). First, a methyl ether at C_{13} was installed using the methyl version of Meerwein's reagent, Me_3OBF_4 to yield **3.26**, then the aromatic bromide was converted to the corresponding trimethylstannane **3.9** in a Stille reaction with hexamethylditin. The same conditions as in the original synthesis were used: 10 mol% $Pd(PPh_3)_4$ as catalyst and Ph_3P as additive to improve the stability of the catalyst in solution, resulted in a yield of 89%. The use of Ph_3As as additive, instead of Ph_3P, did not have a significant effect on reaction rate or yield. The general mechanism of the Stille coupling is depicted in scheme 3.10.[171] The first step is the oxidative addition of the halide **3.42** to the catalyst (Pd(0), **3.43**). Next, the Pd(II) complex **3.43a** can undergo a transmetalation, where the halogen is exchanged for a ligand on the stannyl moiety **3.44**, with formation of a trialkyltin halide **3.45** and **3.43b**. Consequent *trans-cis* isomerization (**3.43c**), sets the stage for reductive elimination to occur, forming again a Pd(0) complex **3.43** and the cross-coupled product **3.46**.



Scheme 3.10: Catalytic cycle of the Stille reaction

3.2.2 Completion of the phenyl analog: macrolactonization approach



a) (*E*)-4-Br-$CH_2CHCHCOOMe$, $Pd_2dba_3.CHCl_3$, THF, 70°C; b) AD-mix β, $MeSO_2NH_2$, $NaHCO_3$, *t*BuOH:H_2O 1:1, RT; c) MOM-Cl, DIPEA, CH_2Cl_2, reflux; d) DDQ, pH7 buffer, CH_2Cl_2, RT; e) $LiOH.H_2O$, THF:H_2O 3:1, RT; f) [i] 2,4,6-trichlorobenzoylchloride, DIPEA, THF, RT; [ii] DMAP, PhMe, RT; g) 4M HCl, THF:H_2O 1:1, RT

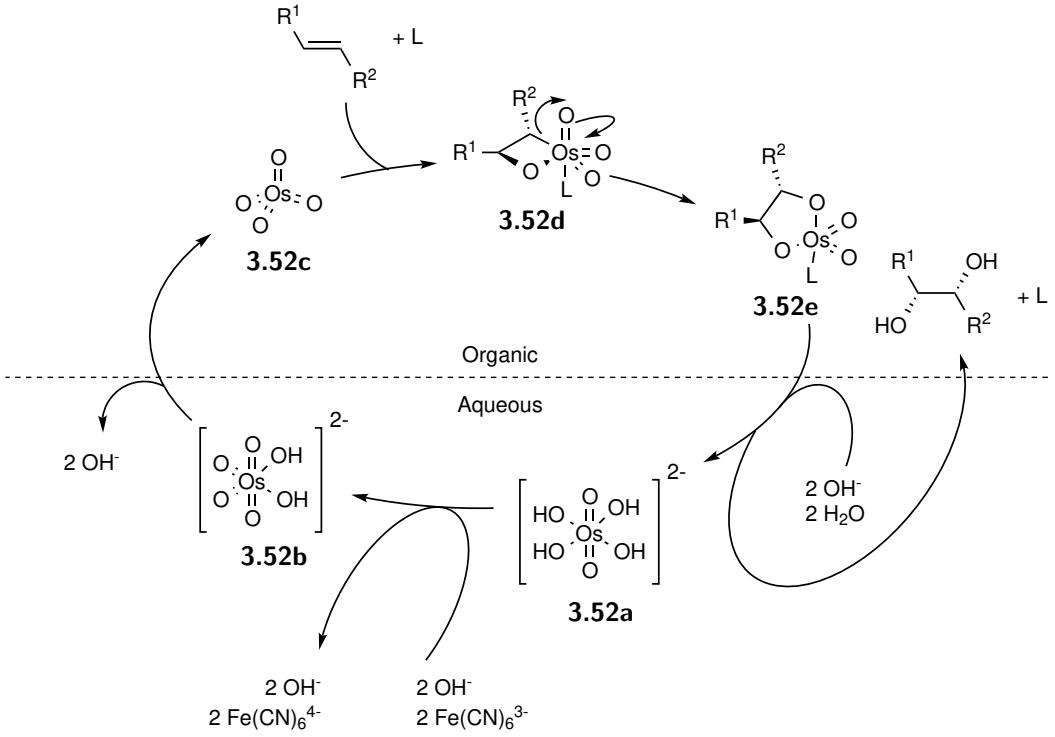
Scheme 3.11: Further elaboration towards pelofen *via* macrolactonization

In a first approach towards the previously synthesized phenyl analog of peloruside A, it was decided to make use of the previously established chemistry.[149] Therefore, the next key steps include again a Stille coupling, an asymmetric dihydroxylation and a macrolactonization (scheme 3.11).

The cross coupling between stannane **3.9** and allylic bromide **3.6**, using $Pd_2(dba)_3 \cdot CHCl_3$ as catalyst, delivered the unsaturated methyl ester **3.47** in 92% yield, together with a minor amount of an isomer where the alkene possesses the *Z*-configuration. This was verified by comparing the coupling constant of the corresponding vicinal alkene protons in the ^{1}H-NMR spectrum: 15.6 Hz for the *E*-isomer, 11.5 Hz for the *Z*-isomer.

The disubstituted olefin in **3.47** was then regioselectively oxidized to diol **3.48** using Sharpless's asymmetric dihydroxylation protocol.[172] As *E*-1,2-disubstituted olefins are regarded as the standard substrate for this protocol, the use of a commercially available premix of all the reagents, the so-called AD-mix, was adequate. This premix contains $K_2OsO_2(OH)_4$ as a non-volatile OsO_4 source, a chiral ligand, *i.e.* bis(dihydroquinidine)phtalazine $(DHQD)_2PHAL$ for AD-mix β or bis(dihydroquinine)phtalazine $(DHQ)_2PHAL$ for AD-mix α, K_2CO_3 to create a basic environment and $K_3Fe(CN)_6$ as co-oxidant. These reagents combined with a biphasic mixture make sure the $OsO_2(OH)_4{}^{2-}$ species (**3.52a**, scheme 3.12) is oxidized to Os(VIII) (**3.52b**) in the aqueous phase, so there is no oxidant other than OsO_4 (**3.52c**) present in the organic layer. Therefore, after osmylation (**3.52d**), the resulting osmium(VI) monoglycolate ester **3.52e** undergoes hydrolysis with formation of the diol and again, an Os(VI) species (**3.52a**). The former stays in the organic phase, while the latter goes directly into the aqueous phase, where the cycle can be repeated.

The formation of the osmium(VI) monoglycolate ester **3.52e** is thought to proceed in a stepwise manner. The first step would then be a [2 + 2]-like cycloaddition of the olefin across an Os = O bond, forming **3.52d**, upon which, in a second step, rearrangement occurs to form the glycolate ester product **3.52e**. Both empirical results and *ab initio* calculations support this mechanism.[173,174] The stereochemical selectivity is evidently determined by choice of the dimeric ligand, which creates



Scheme 3.12: General mechanism of the Sharpless asymmetric dihydroxylation

an enzyme-like binding pocket. The interplay between an attractive stabilization interaction and a repulsive steric interaction creates the bias for facial selectivity. Based on empirical results, Sharpless developed a mnemomic device to predict the stereoselectivity (figure 3.7). According to this model, the use of AD-mix β induces the correct stereochemistry.

The reaction was performed in the presence of $MeSO_2NH_2$ and $NaHCO_3$. The former is known to speed up the reaction, the latter is added to create a buffered system, thereby avoiding hydrolysis of the methyl ester. Diol **3.48** was formed in 88% (isolated yield), with a diastereomeric excess of 97%. The resulting alcohols were protected as MOM- ethers (**3.8**) in 97% yield. Next, the MPM ether at C_{15} was selectively deprotected using DDQ in a biphasic mixture of CH_2Cl_2 and a phosphate buffer at pH 7, resulting in formation of **3.49** in 95% yield.

To obtain the ω-hydroxy acid necessary for macrolactonization, the methyl

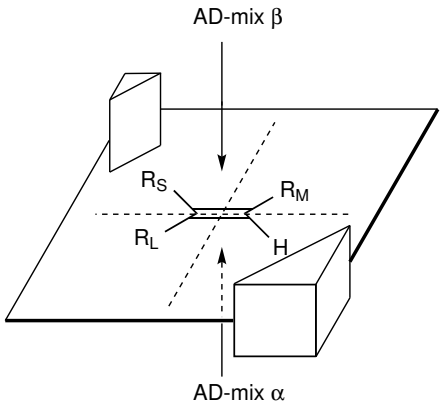
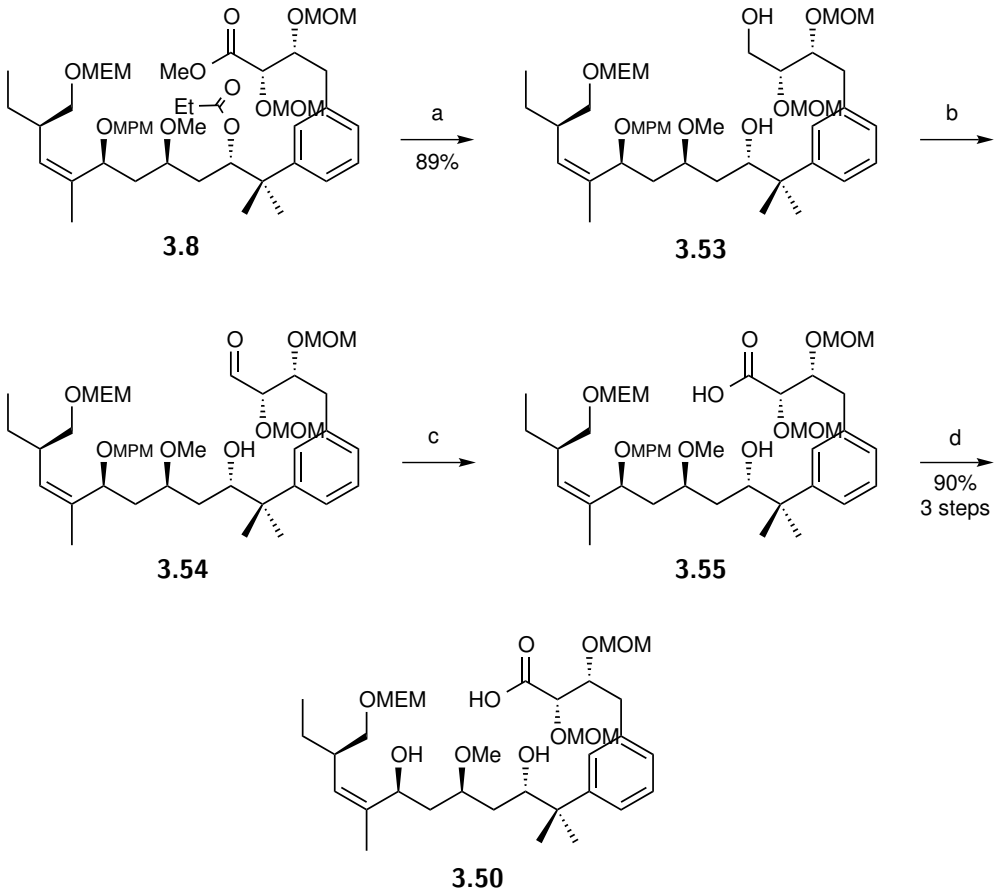


Figure 3.7: Mnemomic device for the prediction of the stereochemical outcome of the SAD

ester must be hydrolyzed. However, also the propionate ester should be removed at this point, as it would be very difficult to remove the latter later on in the synthesis without affecting the macrocyle. Standard, mild conditions (LiOH) did remove the methyl ester easily, but removal of the propionate ester at C_{11} required much longer reaction times. After 7 days, the reaction was not yet finished but 83% of *seco* acid **3.50** could be isolated after flash column chromatography. TLC-analysis showed almost complete conversion after 13 days, without notable formation of epimers. The use of LiOOH, formed *in situ* by combining LiOH and H_2O_2, had an accelerating effect on the hydrolysis of the methyl ester but not on the hydrolysis of the propionate ester. Also the use of potassium hydroxide did not speed up the reaction. A mild procedure, published by Nicolaou employing MeSnOH at elevated temperatures[175] proved to be very slow, even for the hydrolysis of the methyl ester. Another possibility was the transesterification of the propionate ester with MeOH and K_2CO_3, and in a second step, the methyl ester could then be hydrolyzed. However, the transesterification did not work under the tested conditions as the propionate ester was unaffected.

In another approach, which requires two more steps but circumvents the long reaction times, both esters are first reduced, and then, selective oxidation of the primary alcohol provides the required *seco* acid (scheme 3.13). In order to get

a good selectivity, it was decided to postpone the removal of the MPM ether, until after the oxidation of the primary alcohol to the carboxylic acid. In this way, the oxidation procedure only had to distinguish between a sterically hindered secondary alcohol and a primary alcohol, as the secondary allylic alcohol was still protected.

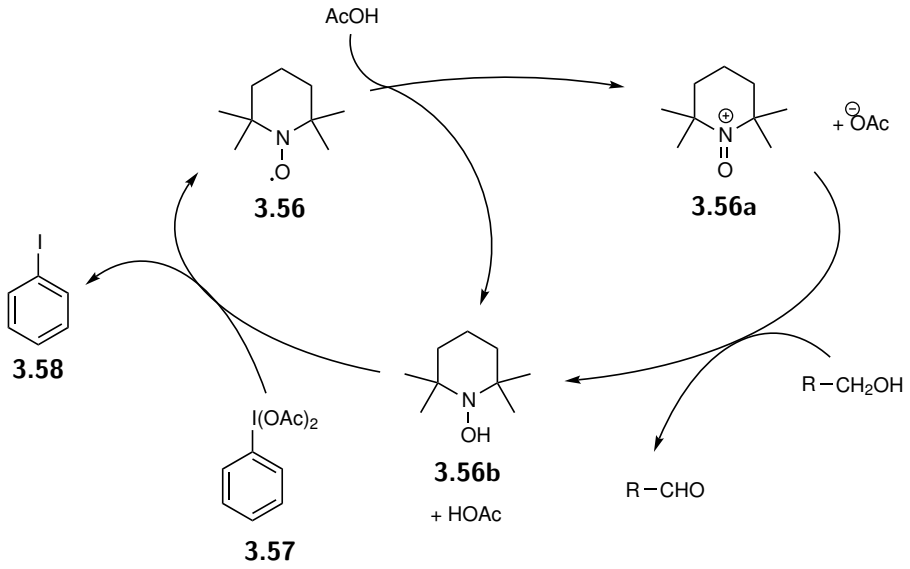


a) $LiAlH_4$, Et_2O, 0°C; b) TEMPO, $PhI(OAc)_2$, CH_2Cl_2,RT; c) NaH_2PO_4, $NaClO_2$, 2-Me-2-butene, *t*BuOH:H_2O 1:1, RT; d) DDQ, pH 7 buffer, CH_2Cl_2, RT

Scheme 3.13: Reduction - oxidation procedure to obtain the *seco* acid **3.50**

Di-ester **3.8** was reduced using $LiAlH_4$ in 89% yield. Next, selective oxidation of the primary alcohol of **3.53** was achieved with catalytic amounts of TEMPO (**3.56**) and bisacetoxy iodobenzene (BAIB) (**3.57**) as terminal oxidant (scheme

3.13).[176]

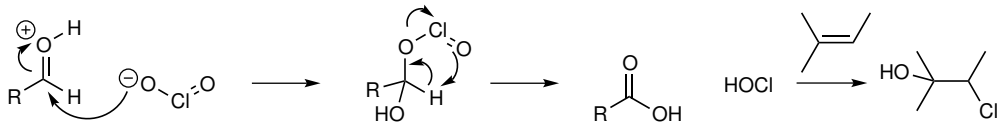


Scheme 3.14: Catalytic cycle for the TEMPO oxidation of alcohols

First, ligand exchange of the alcohol with BAIB generates acetic acid, which is necessary to form the active species. Under the influence of AcOH, TEMPO (**3.56**) disproportionates (dismutation) into an oxoammonium salt **3.56a** and hydroxylamine **3.56b** (scheme 3.14). The former is the primary oxidant, capable of oxidizing the alcohol to the aldehyde, and itself being reduced to hydroxylamine. This is reoxidized by the hypervalent iodine reagent BAIB **3.57**, resulting in the formation of iodobenzene **3.58**, acetic acid and TEMPO.

The product is put crude in the next reaction: a Pinnick-Lindgren oxidation of the aldehyde **3.54** to the carboxylic acid **3.55** (scheme 3.13). Here, by combining $NaClO_2$ with NaH_2PO_4, $HClO_2$ is generated, which can add to the aldehyde (**3.59**, scheme 3.15). Pericyclic fragmentation of the formed adduct **3.60** results in the carboxylic acid and HOCl. The latter product is capable of destroying the $NaClO_2$ reagent, with formation of ClO_2. Therefore, 2-methyl-2-butene is added as a scavenger for trapping the HOCl formed, generating a halohydrin **3.61**.

Several TEMPO-mediated methods exist to oxidize a primary alcohol directly



Scheme 3.15: Mechanism for the Pinnick-Lindgren oxidation of aldehydes to carboxylic acids, with scavenging of HOCl

to the carboxylic acid.[177–179] However, as they all employ an excess of oxidant, they were not tested, out of fear for non-selective oxidation of the alcohol at C_{11}.

Deprotecting the alcohol at C_{15} in **3.55** at the stage of the carboxylic acid occurred without problems, under identical conditions as before, resulting in **3.50** with a yield of 90% over three steps.

Macrolactonization

A crucial step in the synthesis of pelofen (**3.1**) is the formation of the macrocyclic lactone. Numerous methods exist to accomplish this, and there is no generally applicable method which is always successful. On the one hand, the size of the macrocycle is important for ring closure: 4-, 5- and 6-membered lactones are formed rather easily. The medium reactivity of 7-membered lactones is comparable to that of 13- or highered membered macrolactones, whereas the formation of 8- to 11-membered macrolactones is considered to be rather difficult.[180] On the other hand, the possibility to adopt the reactive conformation should be considered: conformationally constrained macrocycles can or cannot possess a preorganisation which leads to smooth, respectively difficult ring closure. Several factors can attribute to these considerations: the mode of activation of the *seco* acid, the presence of protecting groups, sterical hindrance, ... Several examples of macrocyclizations in the total synthesis of natural products are reported in literature.[181,182]

In general, all macrolactonizations can be divided into two categories: addition of the alcohol to an activated carboxylic acid, or nucleophilic attack of the

carboxylate to an activated alcohol (in which the hydroxyl group is converted to a good leaving group). The latter (e.g. Mitsunobu macrolactonization) usually occurs with inversion of the stereochemistry, and thus, is not preferable in our synthesis, as the stereochemistry at C_{15} is already the correct one. Therefore, only methods were tested were the carboxylic acid is activated, as summarized in table 3.2.

Entry	Activating reagent	Remarks	Results
1	2,4,6-trichlorobenzoyl chloride	DMAP	36% yield
2	2,4,6-trichlorobenzoyl chloride	activation diluted, DMAP	31% yield
3	2,4,6-trichlorobenzoyl chloride	DMAP, one pot	16% yield*
4	2,4,6-trichlorobenzoyl chloride	4-pyrrolidino-pyridine, one pot	9% yield*
5	2-methyl-6-nitrobenzoic anhydride	DMAP	no full conversion, 5% yield*
6	2,2'-dipyridylsulfide, PPh_3	80°C	no product observed
7	2,2'-dipyridylsulfide, PPh_3	AgOTf, RT	no product observed
8	2,2'-dipyridylsulfide, PPh_3	AgOTf, 80°C	no product observed
9	1-methyl-2-chloro-pyridiniumiodide	$NaHCO_3$	33% unknown product

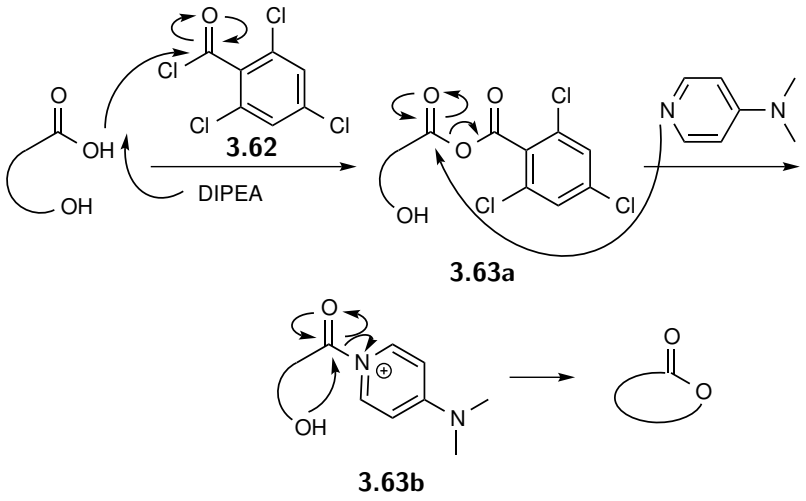
Table 3.2: Some tested conditions for macrolactonization of **3.50**. All experiments were carried out at a dilution of 0.66 mM. (*: based on LC)

In a first series of experiments (table 3.2, entry 1), the Yamaguchi procedure was tested at room temperature (scheme 3.16).[183] Here, the *seco* acid is pre-

activated with 2,4,6-trichlorobenzoyl chloride (**3.62**) to form the mixed anhydride **3.63a**, which then, over a duration of 12h is added *via* syringe pump to a dilute solution (0.66 mM) of DMAP in toluene. In this way, an acylpyridinium species **3.63b** is prone to undergo intramolecular attack of the ω-alcohol. The ring closure does occur, along with formation of some epimers and a lot of dimer, resulting in a modest yield of 36%. MS analysis during the anhydride formation showed that dimer formation already took place during this stage of the cyclization, even in the absence of DMAP. Anticipating this, the activation itself was attempted under dilute conditions (1.3 mM). Unfortunately, did this not result in a decrease of dimer formation (entry 2), nor in a better yield.

Also the use of a one-pot procedure, also known as the Yonemitsu conditions of the Yamaguchi macrolactonization, where both 2,4,6-trichlorobenzoyl chloride, DIPEA and DMAP are combined in one flask and to which a dilute solution of the *seco* acid is added *via* syringe pump,[184] did not show an improvement (table 3.2, entries 3-4). Both the use of DMAP and 4-pyrrolidino-pyridine proved ineffective, as they resulted in more dimer formation. The influence of the temperature using Yamaguchi conditions was not investigated. Although the mechanism is comparable, the use of an alternative benzoic anhydride (2-methyl-6-nitrobenzoic anhydride) can improve the yield of the envisaged cyclized monomer.[185,186] In our case however, no improvement was observed (entry 5). The carboxylic acid was not fully converted, even after prolonged reaction times, resulting in a poor yield of 6%, based on LCMS.

In nature, ester bonds are formed *via* thioesters.[187] This inspired Corey and Nicolaou for the chemical synthesis of macrolactones. First, a thioester **3.64** (scheme 3.17) is synthesized by combining dipyridyl disulfide and PPh_3, which is in essence an oxidation-reduction condensation reaction, reported by Mukaiyama.[188,189] Initial attack of triphenylphosphine on the bipyridyl disulfide will form a phosphonium salt **3.65a**, of which the phosphorus can be attacked by the carboxylic acid with substitution of pyridylthiol and formation of a second phosphonium species **3.65b**. Attack of the pyridyl thiolate anion on the activated carbonyl then generates thioester **3.64** and triphenylphosphine oxide. Once the thioester is formed,



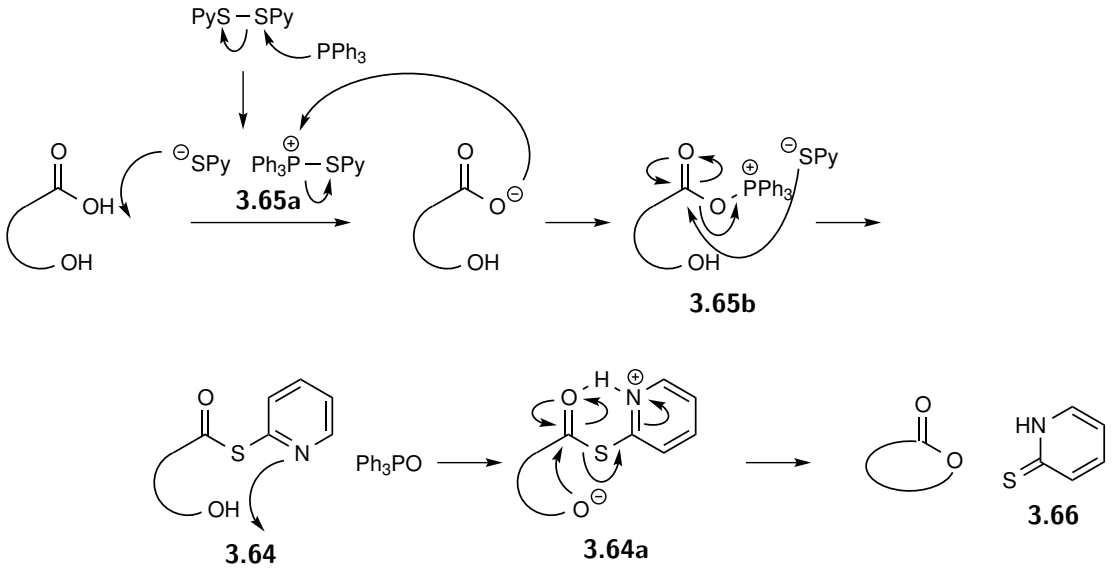
Scheme 3.16: Reaction mechanism of the Yamaguchi macrolactonization

internal proton transfer from the alcohol to the pyridine affords an intermediate **3.64a** in which both the carbonyl and the hydroxyl group are activated, resulting in the macrocyclization and formation of thiopyridone. Therefore, this method is also known as the double activation method, and it is essentially electrostatically driven. The proton transfer itself can be achieved by thermal activation or by metal catalysis. This metal possibly chelates to the sulfur, thereby accelerating the macrolactonization. Gerlach's modification employs silver salts and allows some reactions to be carried out at room temperature.[190]

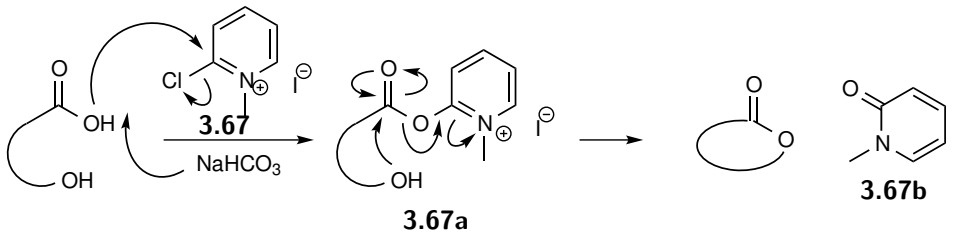
The use of this method for the cyclization of **3.50** however was not a success (entries 6-8).The formation of the thioester was observed in LC-MS, but no macrolactone was detected. Also, it must be said, that the analysis of the mixtures was hampered due to the presence of both triphenylphosphine oxide and thiopyridone.

Another method, employing Mukaiyama's salt (1-methyl-2-chloropyridinium iodide, **3.67**, scheme 3.18) and $NaHCO_3$, was efficient in reducing the amount of dimer.[191] However, LC-MS analysis showed the formation of epimers (different retention time, same mass). The major isomer was isolated (33%) but could not be identified using NMR spectroscopy (table 3.2, entry 9).

The mechanism of this reaction involves chloride substitution by the carboxy-



Scheme 3.17: Reaction mechanism of the Corey-Nicolaou macrolactonization

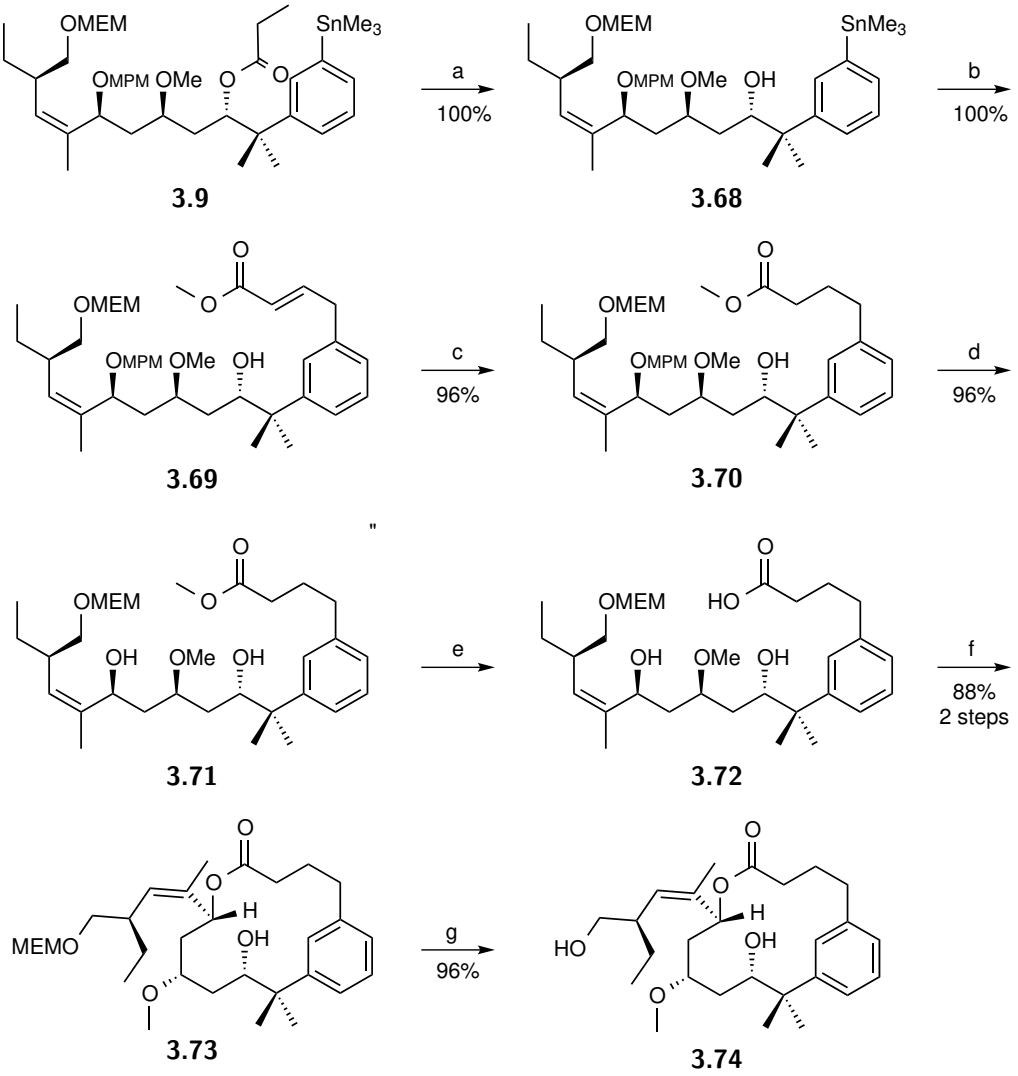


Scheme 3.18: Macrolactonization using Mukaiyama's salt

late anion to give a highly activated acyloxypyridinium species **3.67a**, which then undergoes macrolactonization with formation of N-methyl-2-pyridone **3.67b**.

3.2.3 The synthesis of 2,3-dideoxy pelofen (3.74)

While attempting to find an efficient macrolactonization *en route* to pelofen (**3.1**), an analog lacking the substituents at positon C_2 and C_3 (**3.74**) was synthesized (scheme 3.19). Bearing in mind the earlier encountered problems of ester deprotection, it was decided to first reduce the propionate ester in **3.9**, resulting in stannane **3.68**. Stille reaction employing the same conditions as before delivered



a) $LiAlH_4$, Et_2O, 0°C; b) (*E*)-4-Br-$CH_2CHCHCOOMe$, $Pd_2dba_3.CHCl_3$, THF, 70°C; c) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, 0°C; d) DDQ, pH7 buffer, CH_2Cl_2, RT; e) $LiOH.H_2O$ THF:H_2O 1:1 RT; f) [i] 2,4,6-trichlorobenzoylchloride, DIPEA, PhMe, RT; [ii] DMAP, PhMe, RT; g) *n*-BuSH, $ZnBr_2$, CH_2Cl_2, RT

Scheme 3.19: Synthesis of the 2,3-dideoxy analog (**3.74**) of pelofen

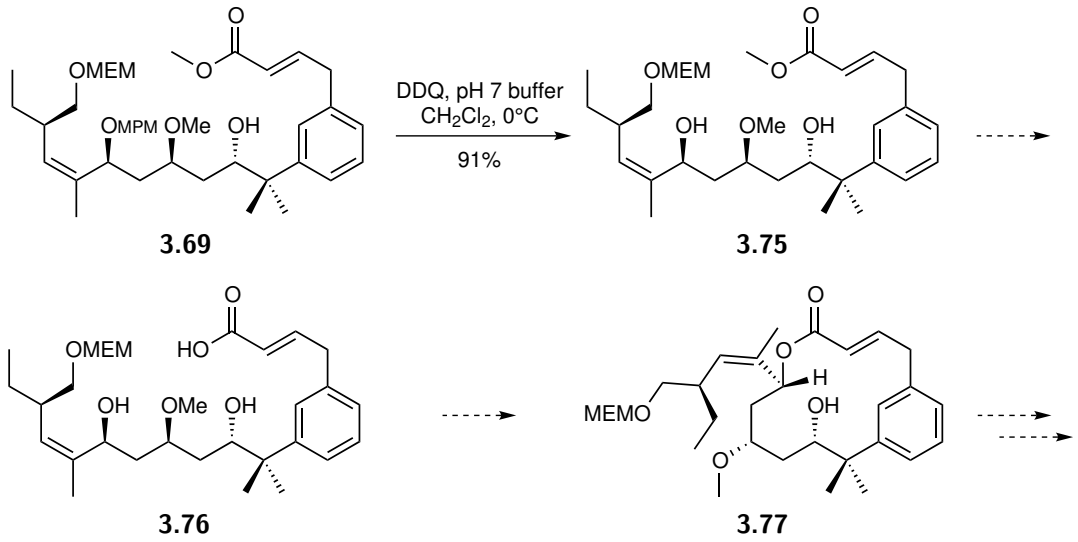
unsaturated ester **3.69** nearly quantitatively, without observation of the *Z* isomer. Next, the conjugated double bond was regioselectively saturated to ester **3.70** using $NaBH_4$ and catalytic amounts of $NiCl_2.6H_2O$ in MeOH.[192,193] The exact mechanism of this reaction is unknown: both the *in situ* formation of Ni_2B and H_2 or the generation of a nickel hydride could account for the active species.[194]

The MPM ether in **3.70** was removed with DDQ (96% yield) and the remaining methyl ester was hydrolysed to obtain the ω-hydroxy acid necessary for ring closure. The first attempt to close the macrocycle, by applying Yamaguchi's conditions, *via* preparation of the mixed anhydride in toluene and then addition to a diluted solution of DMAP in toluene (0.66 mM) delivered **3.73** in 88% over two steps, without dimer formation or epimerization. The final deprotection of the primary alcohol proceeded smoothly in 96% yield, making use of $ZnBr_2$ as Lewis acid and a thiol as scavenger.

Compound **3.74** was tested for its biological activity by professor Bracke (laboratorium for experimental cancer research) in two different assays on MO4 cells. These cells are murine, virally transformed fibrosarcoma-like cells, which are highly invasive, tumorigenic in a specific mouse, and sensitive to microtubule inhibitors. Because of these features, they are an ideal model for cancer *in vitro*. The MTT assay is a measure for the viability of the cell, correlated with the metabolic events that lead to apoptosis or necrosis of the cell.[195] Sulforhodamine B (SRB) is an anionic dye that binds to proteins electrostatically. The fixed dye, measured photometrically after solubilization, correlates with total protein synthesis rate and therefore with cell proliferation.[196]

Unfortunately, no statistically significant results could be obtained so far. Therefor, no conclusions about the importance of the substituents at the C_2 and C_3 position could be drawn.

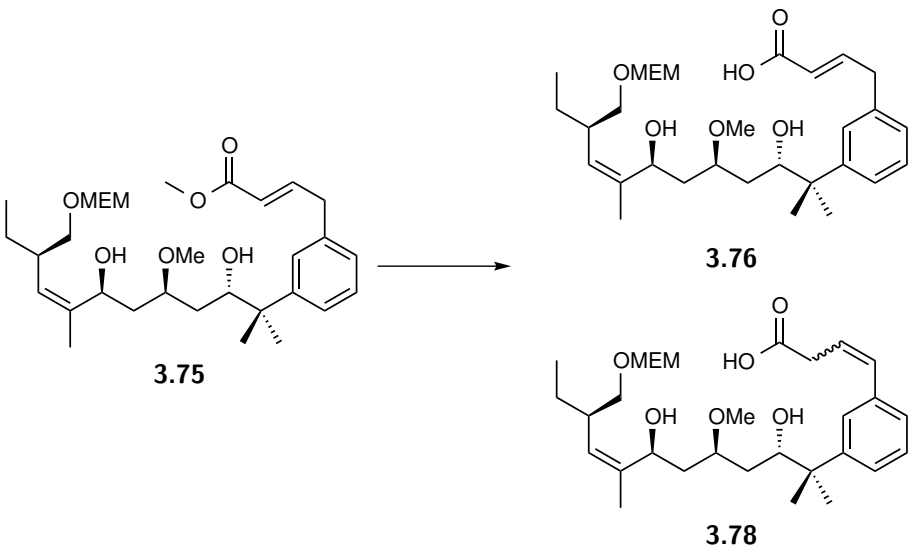
3.2.4 New route to pelofen and analogs at the C_2-C_3-position



Scheme 3.20

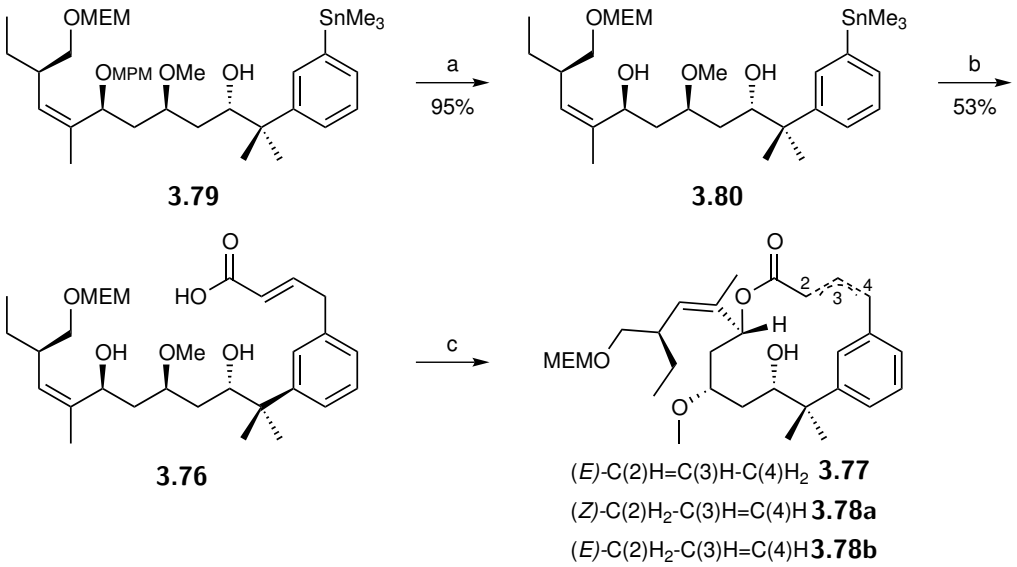
Although the 2,3-dideoxy-analog was not active, its synthesis opened possibilities for the synthesis of pelofen (**3.1**) and other analogs with modifications in the C_2-C_3-region. As the macrolactonization of *seco* acid **3.72** without substituents at C_2 and C_3 proceeded without difficulties, it was considered to ring close the unsaturated ω-hydroxy acid **3.76** (scheme 3.20). Late stage dihydroxylation of the conjugated olefin would then install the alcohols at C_2 and C_3, and deprotection of the primary alcohol at C_{24} would immediately result in **3.1**.

The removal of the MPM proceeded as planned (scheme 3.20). However, upon hydrolysis of the methyl ester, using LiOH, the olefin partly migrated towards the phenyl ring to form a mixture of the envisaged conjugated carboxylic acid **3.76** and styrene-like derivatives **3.78** (scheme 3.21). Upon use of the earlier reported, milder hydrolysing agent Me_3SnOH, the reaction was complete in 24h, but the migration was not prevented, and a similar mixture was obtained.



Scheme 3.21: Isomerization of the conjugated ester to the styrene derivative **3.78**

As the double bond migration occured only at the time of hydrolysis, and not during the preceding Stille coupling, we considered to directly install the carboxylic acid *via* Stille reaction (scheme 3.22). Therefore, the MPM ether of stannane **3.79** was removed easily, and the resulting stannane **3.80** was coupled with *E*-4-bromo crotonic acid under Pd(0)-catalysis. In this way, the amount of migration was restricted to a minimum. However, this time, destannylation occurred as a side reaction. The addition of an excess of DIPEA to neutralize the acid resulted in a complex mixture, which unfortunately still contained the destannylated product. The isolated yield of carboxylic acid **3.76** was therefore limited to 53%. Nevertheless, with pure **3.76** in hand, the macrolactonization was attempted, under exactly the same conditions as with the dideoxy analog. In this case, not only a significant amount of dimer was formed, but also migration of the double bond was observed, probably caused by the basic conditions during the Yamaguchi macrolactonization. The yield was not determined, but the main product was identified to be the styrene derivative possessing the *Z* configuration (**3.78a**) (scheme 3.22).



a) DDQ, pH7 buffer, CH_2Cl_2, RT; b) (*E*)-4-Br-CH_2CHCHCOOH, Pd_2dba_3.$CHCl_3$, THF, 60°C; c) [i] 2,4,6-trichlorobenzoylchloride, DIPEA, PhMe, RT; [ii] DMAP, PhMe, RT

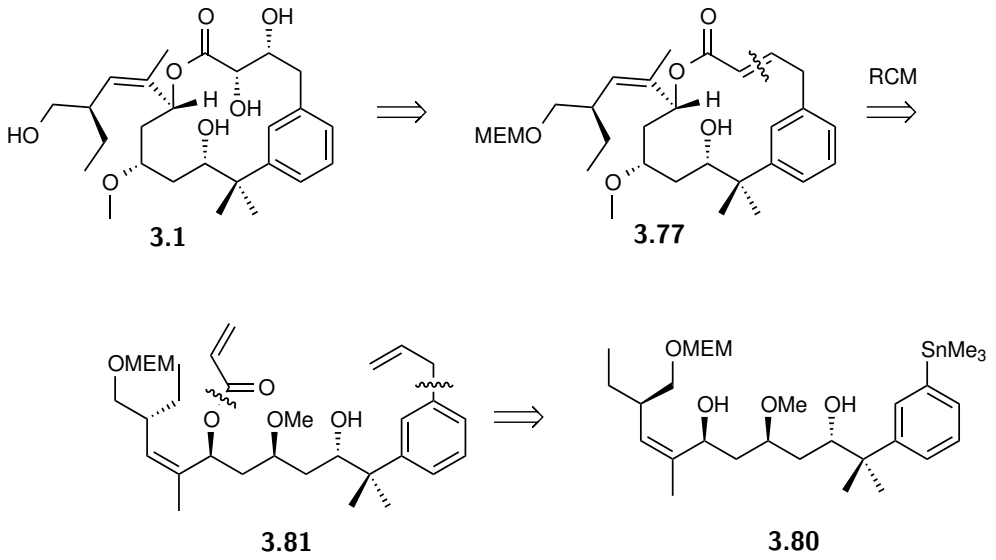
Scheme 3.22

3.2.5 Diversification of phenyl analogs: Ring-Closing Metathesis approach

As the envisaged target could not be obtained in an acceptable yield via macrolactonization, another approach was attempted: the ring-closing metathesis. A retrosynthetic analysis is represented in scheme 3.23.

Two reactions are essential in synthesizing the diene precursor for the ring-closing metathesis: the allylation through Stille coupling of **3.80** to afford **3.82** and the acryloylation of **3.80** to acryloyl ester **3.83** (scheme 3.24). Initially, these two reactions were optimized simultaneously.

A first test for the Stille coupling, employing allyl bromide in THF and Pd_2dba_3. $CHCl_3$ as catalyst, again resulted in partial migration of the olefin to obtain conjugation with the aromatic ring. Therefore, efforts were made to suppress the isomerization, summarized in table 3.3. Judged by TLC and LC analysis, the



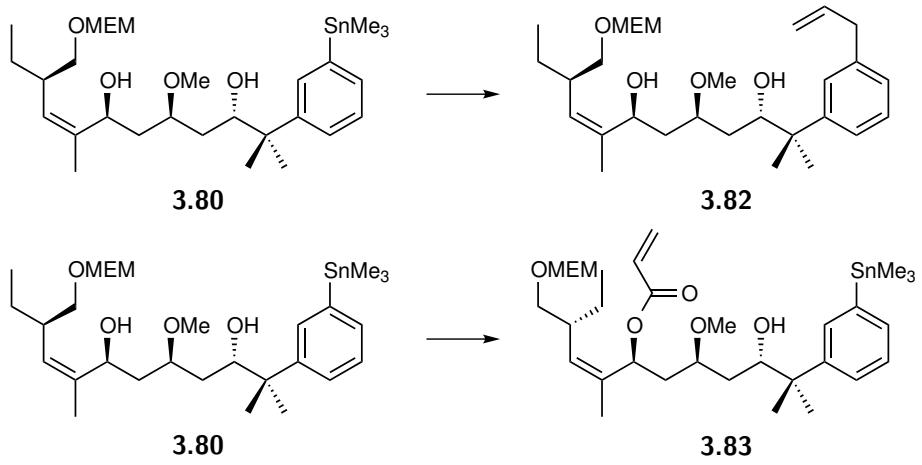
Scheme 3.23: Retrosynthetic analysis of **3.1** *via* ring-closing metathesis

reaction in pure allylbromide (entry 4) was the cleanest, minimizing isomerization and formation of by-products.

Entry	catalyst	# eq. catalyst	solvent	T (°C)	time	%isomer
1	$Pd_2dba_3.CHCl_3$	0.05	THF	60	90 min	23
2	Pd_2dba_3	0.05	THF	60	90 min	15
3	$[allylPdCl]_2$	0.15	THF	60	30 min	5
4	$Pd_2dba_3.CHCl_3$	0.05	*neat*	60	30 min	4
5	$Pd_2dba_3.CHCl_3$	0.05	THF	21	12 h	9

Table 3.3: Cross coupling conditions for the aryl allylation with allyl bromide

The introduction of the acryloyl group in **3.68** was thought to be straightforward, even in the presence of two free hydroxyl groups, as there is a big difference in sterical environment between both. However, the reaction turned out to be unselective, as reaction with acryloyl chloride resulted in double esterification (in a 1:1 ratio). Yamaguchi esterification (acrylic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP) was selective, but inefficient, as the reaction did not run to

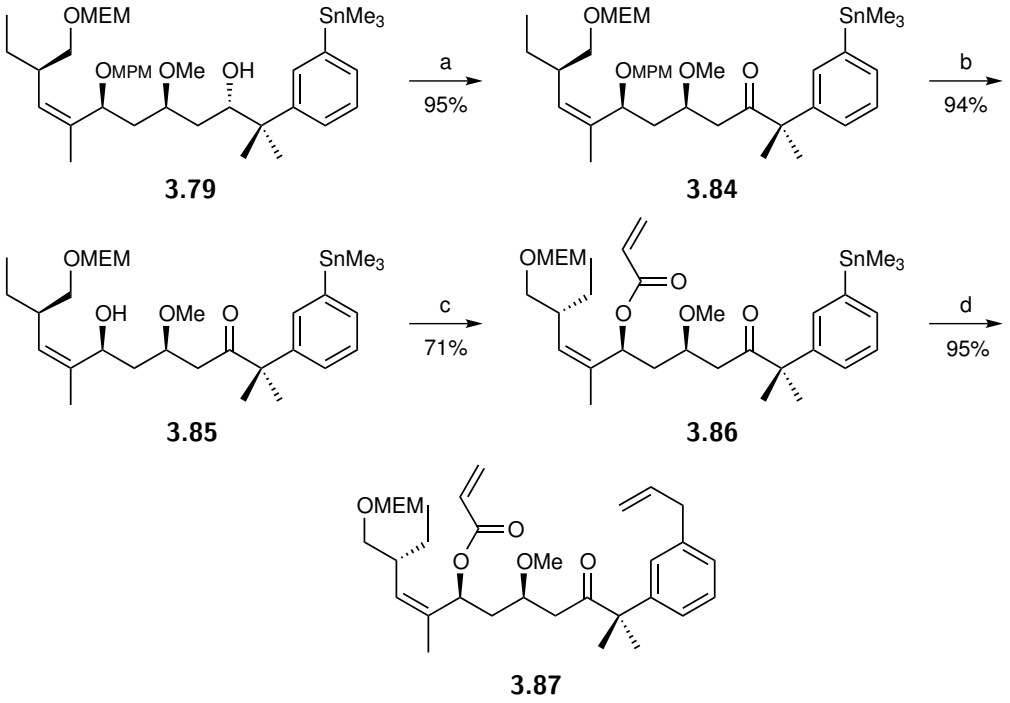


Scheme 3.24: Key steps in the synthesis of diene **3.81**

completion. Steglich esterification, employing acrylic acid, EDCI.HCl and DMAP, required long reaction times (several days), but gave a clean, spot-to-spot reaction on TLC, in favor of the required mono-ester **3.83**. After isolation however, the yield proved to be only 10%.

To avoid the problems associated with the double esterification, we decided to oxidize the alcohol at C_{11} to the ketone. This way of 'protecting' the alcohol opened up the additional possibility to gain access to analogs with variations on this C_{11}. For instance, stereoselective reduction or reductive amination could introduce both epimeric alcohols, respectively amines, whereas Wolff-Kishner reduction could remove the substituent at C_{11}.

Ley-Griffith oxidation of **3.79** (scheme 3.25) using catalytic perruthenate and NMO proved to be superior over Swern oxidation, giving **3.84** in 95% yield. The subsequent deprotection of the C_{15} allylic alcohol to **3.85** proceeded in a comparable yield. The acrylation however, again, caused some difficulties. Performing the reaction with pure acryloyl chloride and DMAP as base (entry 1, table 3.4) did only give trace amounts of **3.86**, but the starting material could be recuperated. Making use of Et_3N as base and DMAP as nucleophilic catalyst and a large excess of the acid chloride gave full conversion. However, after column chromatography, only 30% could be isolated (entry 2). Omitting DMAP from the reaction mixture



a) TPAP, NMO, 4Â molecular sieves, CH_2Cl_2,RT; b) DDQ, pH7 buffer, CH_2Cl_2, 0°C; c) $CH_2CHCOCl$, DIPEA, CH_2Cl_2, RT, 0°C; d) CH_2CHCH_2Br, $Pd_2dba_3.CHCl_3$, 60°C

Scheme 3.25: Synthesis of diene **3.87**, the precursor for ring-closing metathesis

and adding the acid chloride as a 0.1M solution in CH_2Cl_2, resulted in a good crude yield (entry 3), which was not purified and put into the next reaction. However, the yield after the next step was lower than expected, probably because the isolated yield of **3.86** was much lower than the crude yield. Next, DIPEA was used as base, and the reaction was started with 5 equivalents of acid chloride (again as a solution in CH_2Cl_2). As the starting material **3.85** was not fully converted (as evaluated by TLC analysis), another 2.5 equivalents were added after 3h. Still, this gave no full conversion, but the starting and target material were separated by means of column chromatography, resulting in 86% of ester **3.86**, and 9% of recovered alcohol **3.85**. In order to get full conversion, the reacion was performed with 10 equivalents of acid chloride from the start (as in entries 2 and 3). This time however, the starting material was again not fully converted, and the yield

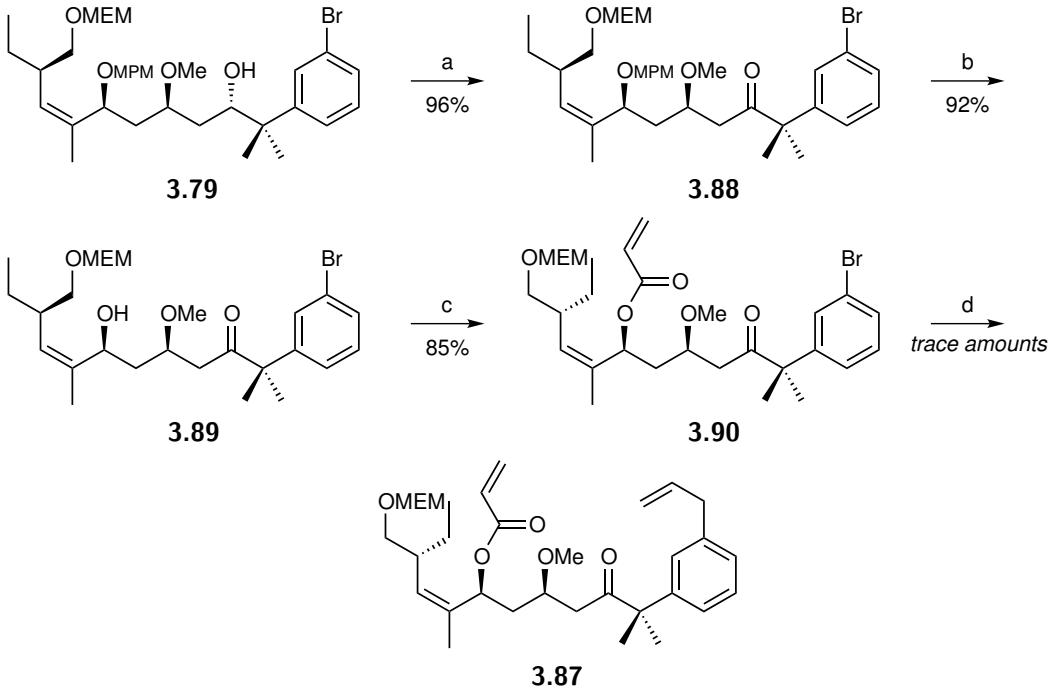
was even lower than in case of portion-wise addition (entry 5). Introduction of the arylic allyl group was achieved by applying the previously optimized method ($Pd_2dba_3.CHCl_3$ in neat allyl bromide), yielding diene **3.87** in 95%, without notable migration of the olefin to form the styrene-derivative.

Entry	base	$CH_2CHCOCl$	eq. RCOCl	observations	yield
1	DMAP	*neat*	2	trace amounts of **3.86**	<1%
2	Et_3N, DMAP	*neat*	10	full conversion	30%
3	Et_3N	0.1M in CH_2Cl_2	10	full conversion	99% crude
4	DIPEA	0.1M in CH_2Cl_2	5 + 2.5	no full conversion	86% (95% brsm)
5	DIPEA	0.1M in CH_2Cl_2	10	no full conversion	71% (84% brsm)

Table 3.4: Tested conditions for the acryloylation of **3.85** (brsm: based on recovered starting material)

Efforts were also undertaken to develop an alternative synthesis of diene **3.87**, where the original arylic bromide is maintained throughout the synthesis (scheme 3.26). Thus, the bromide does not have to be converted to the stannane, which reduces the number of steps, as the bromide can be directly coupled with an allyl group in a Suzuki or Stille reaction. This last step still has to be optimized, as only trace amounts were detected in preliminary experiments, employing either allyl-pinacolboronate, CsF and $PdCl_2(dppf).CH_2Cl_2$ for the Suzuki coupling, or allyl-tributyltin and $Pd(PPh_3)_4$ for the Stille reaction.

With diene **3.87** in hand, the ring-closing metathesis reaction could be tested.



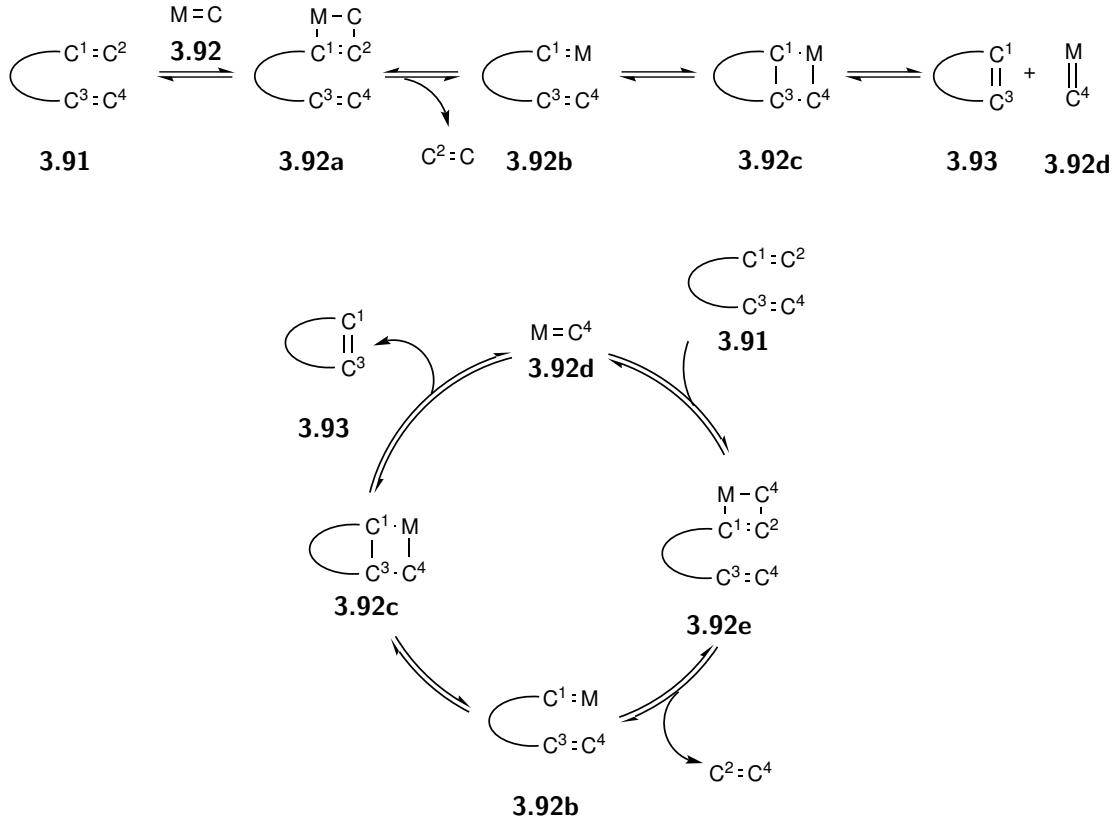
a) TPAP, NMO, 4Â molecular sieves, CH_2Cl_2,RT; b) DDQ, pH7 buffer, CH_2Cl_2, 0°C; c) $CH_2CHCOCl$, DIPEA, CH_2Cl_2, RT, 0°C; d) Stille or Suzuki reaction

Scheme 3.26: Alternative synthesis of diene **3.87**

Ring-closing metathesis

Olefin metathesis is the net transposition of fragments of alkenes, by the scission and regeneration of carbon-carbon double bonds.[197] Ring-closing metathesis is a specific type, where two alkenes react with a catalyst, in order to generate a (macro)cyclic olefin.[198–200] The reaction is driven to completion because volatile products are formed and removed.

Transition metal-catalyzed metathesis was originally observed in industry in the 1950's, mainly in polymerization reactions. The reaction mechanism, however, remained a mystery until Chauvin in the 70's published his proposal, based on the previously observed findings and supported by new experiments.[201]



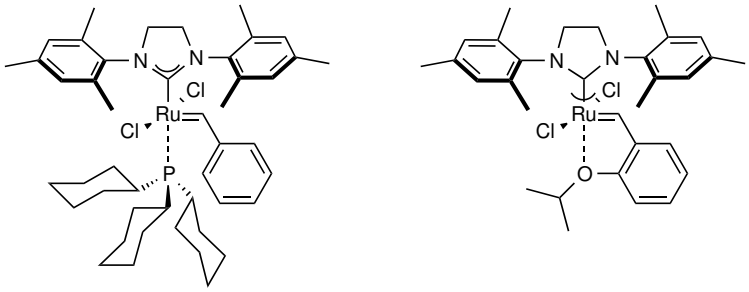
Scheme 3.27: Chauvin's reaction mechanism for the ring-closing olefin metathesis

The catalytic cycle consists of an initiation phase (scheme 3.27, top), where the active complex is generated, and a propagation phase (scheme 3.27, bottom), which is repeated until the starting diene is consumed, or an equilibrium is reached. In the initiation step, an olefin of the substrate **3.91** reacts with the metal alkylidene **3.92** in a [2+2] cycloaddition, to generate a metallocyclobutane **3.92a**. Next, a [2+2] cycloreversion creates a new (substrate-loaded) metal alkylidene **3.92b**, with expulsion of an olefin, of which one alkylidene is coming from the catalyst (C) and one is coming from the starting material (C^2). The newly formed metal alkylidene **3.92b** again can undergo a cycloaddition to the other olefin of the diene to form a new metallocyclobutane **3.92c**, which can in turn disintegrate in the forward direction to form the cyclized product **3.93** and a new, metal alkylidene **3.92d**. The latter acts as the active catalyst in the catalytic cycle, where another series

of cycloaddition/cycloreversion events leads to the cyclization product **3.93** and the active species **3.92d**.

From this mechanism, which relies on a metal alkylidene initiating the metathesis, Chauvin suggested that catalysis by -on purpose- synthesized metal-alkylidene complexes could efficiently induce metathesis reactions. Synthesis of these types of catalyst was mainly done by Schrock and Grubbs, who, together with Chauvin, received the Noble Prize in 2005 '*for the development of the metathesis method in organic synthesis*'.[202]

While the catalysts developed by Schrock are based on molybdenum or tungsten, those developed by Grubbs are based on ruthenium. In general, the Ru-based catalyst are more compatible with functional groups and more stable to air and moisture. Several of them are commercially available, two of which were tested: Grubbs 2nd generation catalyst (**3.94**) and Hoveyda Grubbs 2nd generation catalyst (**3.95**), which are depicted in figure 3.8.

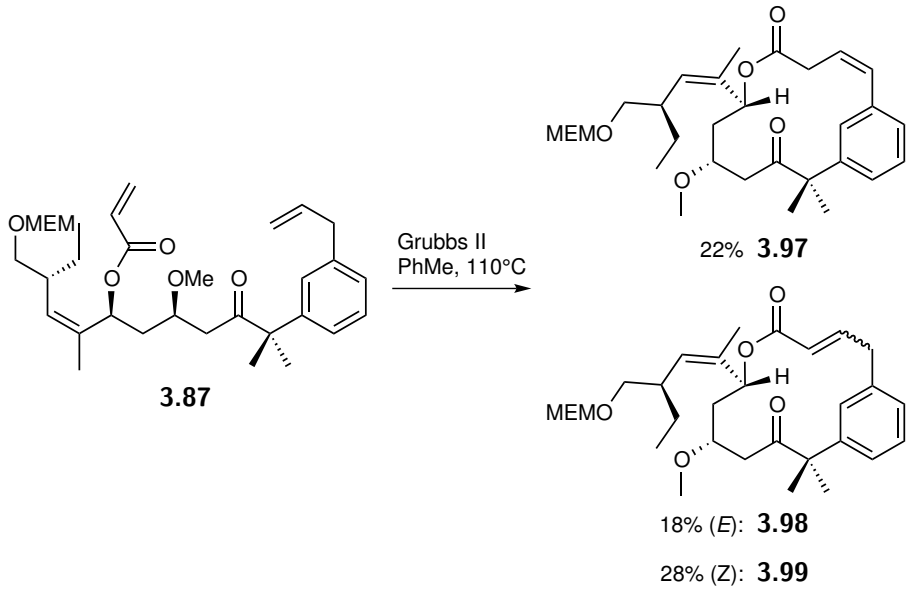


3.94 **3.95**

Figure 3.8: Structure of the Grubbs (**3.94**) and Hoveyda-Grubbs's (**3.96**) 2nd generation catalysts

The reaction was optimized in function of conversion and in function of cyclic monomer formation, compared to the formation of oligomers (diolide, or even triolide). As also cross metathesis can occur, in which an olefin from the diene is coupled to an olefin of another diene molecule, different types of dimer can be formed: head-to-head coupling as well as head-to-tail coupling is possible. Moreover, the dimers can exist in an open form as well as in their closed form.

The reactions were tested on a 0.5-1 mg scale of diene **3.87**, and executed under high dilution to avoid oligomer formation. From TLC- and LC analysis, a few conclusions could be drawn (table 3.5) First, toluene proved to be a better solvent than CH_2Cl_2 as it gave a cleaner reaction (entries 1-3). Next, it seemed that the Hoveyda-Grubbs catalyst **3.96** was too reactive, as significantly more oligomers were formed, while the amount of desired monomer was moderate to low (entries 3-5). Using the Grubbs catalyst **3.94**, the influence of the temperature was investigated (entries 6- 7). The best result was obtained when performing the reaction at higher temperature (110°C) in PhMe (entry 7). Applying the same conditions for a shorter reaction time (entry 8) resulted in less monomer formation, although the starting material was almost fully converted. This suggested an equilibrium between oligo- and monomer can set in in function of time. Therefore the conditions were repeated in an even more dilute system, but again with different reaction times. (entries 9-10). However, no clear relationship between reaction time and monomer formation could be observed. The use of a lower amount of catalyst (entry 11) did not give significant differences.



Scheme 3.28: Result of the ring-closure metathesis on a 17 mg scale

The reaction was then performed on a slightly bigger scale (17 mg) using 10 mol% Grubbs 2nd generation catalyst, 1mM solution in toluene, 15 min reaction time (scheme 3.28). LC indicated good conversion (98%) and around 70% monomer yield. After multiple column chromatographic purifications however, 3 compounds were isolated: 18% of the *E*-isomer **3.98**, 28% of the *Z*-isomer **3.99** and 22% of the styrene-derivative **3.97**. The migration of the double bond towards this styrene-derivative was not observed in the test reactions, at least not to this extent, as the peaks in the chromatogram overlap. The configuration of the double bond in **3.97** was established to be *Z*, based on the coupling constants between the vicinal protons (^{3}J = 11.5 Hz).

These results indicate this route can be used to generate quickly several analogs, with modifications in the C_2-C_4 region. However, in order to set a straightforward route towards pelofen **3.1**, the final ring-closing metathesis step needs further optimization. Also, the transformation of the double bond into other functional groups needs further research.

Entry	catalyst	amount of catalyst	solvent	T	dilution	conversion	time	% monomer
1	**3.96**	50 mol%	CH_2Cl_2	RT	1mM	75%	24h	22%
2	**3.96**	50 mol%	CH_2Cl_2	40°C	1mM	99%	24h	29%
3	**3.96**	14 mol%	PhMe	40°C	1mM	100%	21h	25%
4	**3.96**	14 mol%	PhMe	70°C	1mM	100%	21h	29%
5	**3.96**	14 mol%	PhMe	110°C	1mM	99%	90'	4%
6	**3.94**	10 mol%	PhMe	40°C	1mM	87%	17h	40%
7	**3.94**	10 mol%	PhMe	110°C	1mM	98%	17h	79%
8	**3.94**	10 mol%	PhMe	110°C	1mM	>95%	5'	32%
9	**3.94**	10 mol%	PhMe	110°C	0.5mM	99%	15'	69%
10	**3.94**	10 mol%	PhMe	110°C	0.5mM	99%	90'	53%
11	**3.94**	5 mol%	PhMe	110°C	1mM	98%	15'	69%

Table 3.5: Test reactions for the ring-closing metathesis of diene **3.87**

4

Conclusions and future perspectives

4.1 Aims

Peloruside (**4.1**, figure 4.1) is a natural product which shows cytotoxic activity at nanomolar concentrations. More importantly, it acts as a microtubule stabilizer in a similar way as paclitaxel, a well established chemotherapeutic. Because of its low natural abundancy and complexity, peloruside cannot be used as such in the clinic. To explore the potential of this natural product, SAR analysis can be of use to come up with more simplified analogs that retain their activity. Therefore, in this thesis, attempts were made to investigate the importance of the substituents on the pyranose ring of peloruside by making simplified analogs **4.2**. Our aim was to construct the THP-ring through application of the Mukaiyama aldol - Prins reaction. (Chapter 2)

On the other hand, the synthesis of a simplified analog, pelofen B (**4.3**), in which the full pyranose ring has been replaced by a phenyl ring, developed in our lab, was re-evaluated to come up with a more straightforward synthesis, which would allow access to analogs with varied functional groups. (Chapter 3)

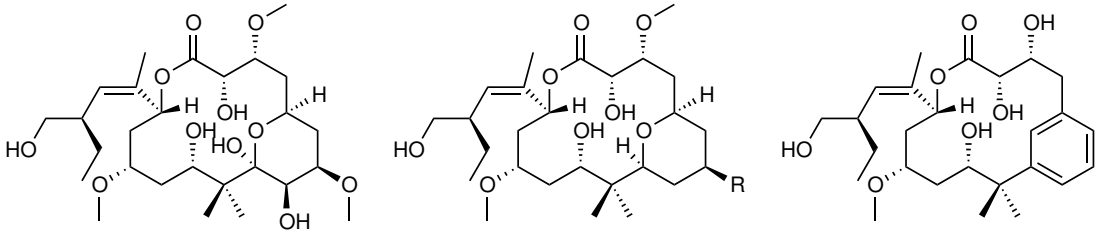


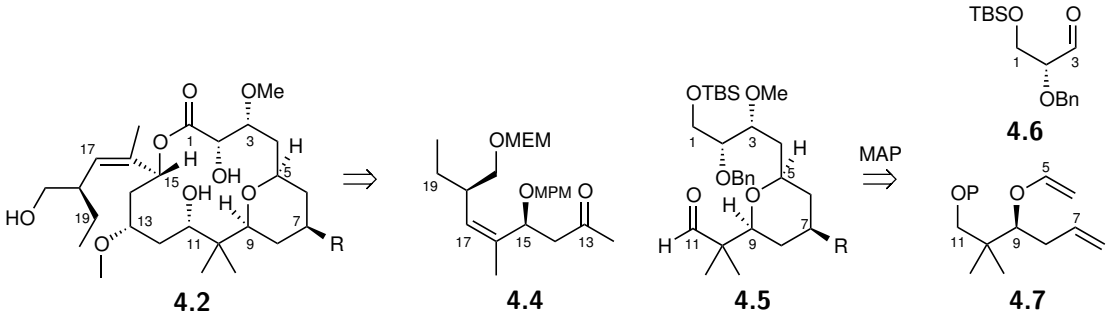
Figure 4.1

4.2 Tetrahydropyran analogs

4.2.1 Results

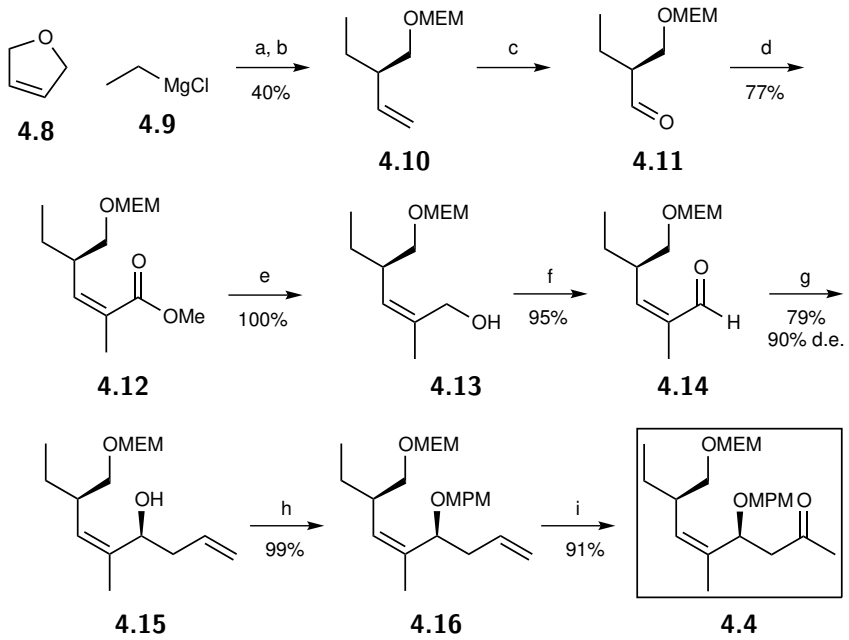
Our design for the synthesis of THP-analogs **4.2** (scheme 4.1) was based on the aldol coupling of two advanced intermediates: a methyl ketone **4.4**, containing two

stereocenters and the trisubstituted olefin of the side chain, and an aldehyde **4.5**, containing the THP ring and two additional stereocenters. The synthesis of the latter fragment was based on the Mukaiyama aldol - Prins (MAP) cyclization, a cascade reaction between an aldehyde **4.6** and a bisnucleophile **4.7**, in the presence of a Lewis acid.



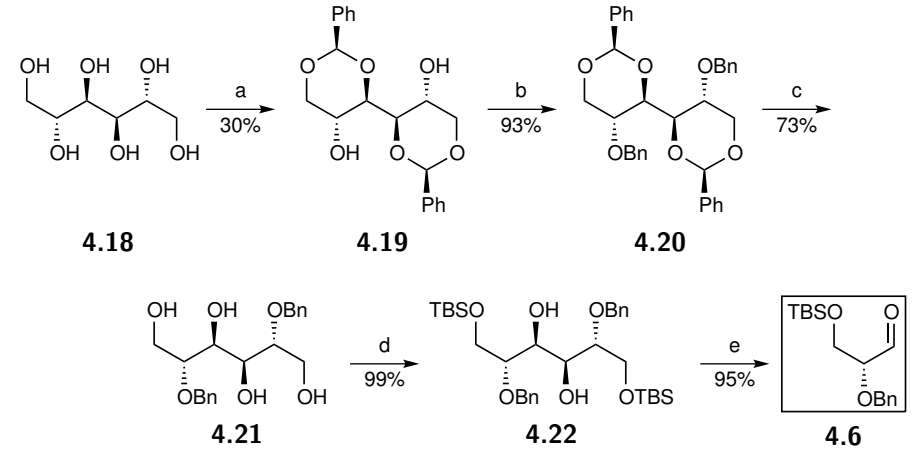
Scheme 4.1: Retrosynthetic analysis of the envisaged THP analogs

The synthesis of the $C_{12}-C_{20}$ fragment **4.4** (scheme 4.2) started with the carbomagnesation of dihydrofuran (**4.8**) with ethylmagnesium chloride (**4.9**), in a zirconium-catalysed reaction, which proceeded with excellent enantioselectivty (>98:2). The resulting homoallylic alcohol was protected as an acetal, and the olefin was oxidatively cleaved by ozone, delivering aldehyde **4.11**. The *Z*-double bond was constructed using phosphonate **4.17** in a modification of the Horner-Wadsworth-Emmons reaction, developed by Still and Gennari. The geometry of the double bond was confirmed by NOE spectroscopy. A reduction-oxidation procedure delivered aldehyde **4.14** which could be stereoselectively allylated in a Brown allylation reaction. Both isolated yield (79%) and diastereomeric excess (90%) of this reaction were satisfying. The stereochemistry of the carbinol in **4.15** was assigned using Mosher-ester analysis. After protection of the resulting homoallylic alcohol **4.15** as MPM-ether, the terminal olefin was selectively oxidized to the methyl ketone **4.4** in a Pd-catalyzed Wacker oxidation. Overall, this building block was synthesized in a linear sequence of 9 steps with a total yield of 21%. This somewhat lower yield is basically due to the first step (40%), which was optimized in terms of catalyst turnover number.



a) [(*S,S*)-ethylene-bis(4,5,6,7-tetrahydro-1-indenyl)]Zr(IV)BINOL , THF, 40h, RT; b) DIPEA, MEM-Cl, CH_2Cl_2, reflux; c) [i] O_3, CH_2Cl_2, -78°C; [ii] Ph_3P, CH_2Cl_2; d) 18-crown-6, KHMDS, THF, -78°C, $(CF_3CH_2O)_2POCH(CH_3)CO_2CH_3$; e) DIBAL-H, CH_2Cl_2, -78°C, 1h; f) DMP, pyridine, CH_2Cl_2, 1h, rt; g) [i] (-)-Ipc$_2$BOMe, allylMgBr, Et_2O, -78°C; [ii] NaOH, H_2O_2, RT; h) [i] NaH, THF, 0°C; [ii] MPM-Cl, TBAI, DMF, RT; i) $PdCl_2$, $Cu(OAc)_2.H_2O$, DMF:H_2O 9:1, O_2, RT

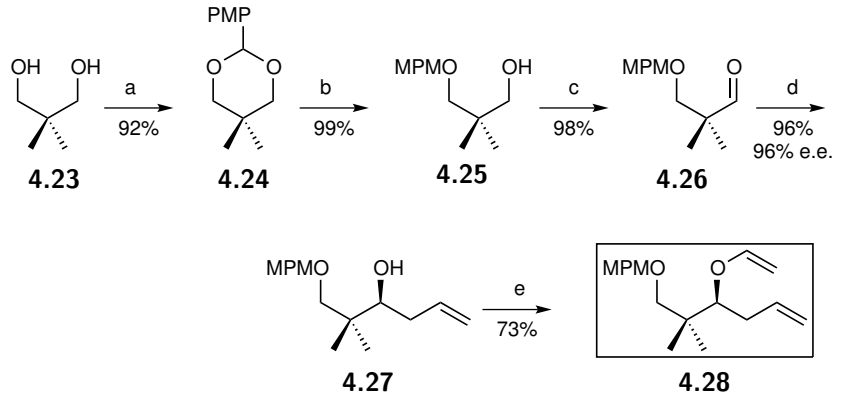
Scheme 4.2: Synthesis of the C_{12}-C_{20} fragment **4.4**



a) PhCHO, H_2SO_4, DMF, RT; b) KOH, DMSO, BnBr, RT c) HCl, MeOH/C_6H_{14} 5/3, RT; d) TBSCl, imidazole, CH_2Cl_2, RT; e) $NaIO_4$, THF/H_2O 4/1, RT

Scheme 4.3: Synthesis of aldehyde **4.6**

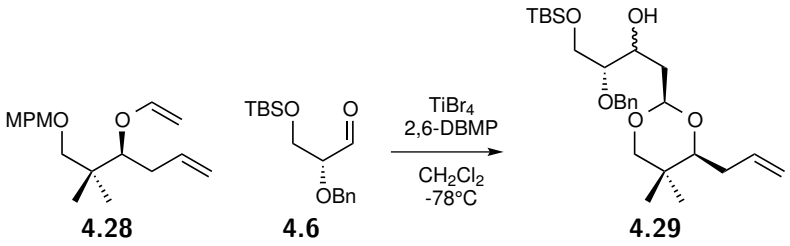
The second fragment **4.5** is comprised of two building blocks itself. The first one, aldehyde **4.6**, is obtained from D-mannitol, of which 4 hydroxyls were protected with benzaldehyde as 1,3-4,6 bis-benzylidene acetal **4.19** in 30% yield (scheme 4.3). The remaining alcohols were benzylated, after which the benzylidene acetals were removed again, to provide tetrol **4.21**. The primary alcohols were selectively protected as silyl ether, to form bis-silyl ether **4.22**. Oxidative cleavage of the remaining diol was achieved with sodium periodate and afforded aldehyde **4.6** in 19% yield over 5 steps.



a) 4-MeO-PhCH(OMe)$_2$, CSA, CH_2Cl_2, RT; b) $LiAlH_4$, $AlCl_3$, Et_2O, -10°C; c) [i] $(COCl)_2$, DMSO, -78°C [ii] Et_3N, CH_2Cl_2, -78°C; d) $[Ir(cod)Cl]_2$, (*S*)-(-)-Cl, MeO-BIPHEP, Cs_2CO_3, 4-Cl-3-NO_2-benzoic acid, THF, allylOAc, 2-PrOH, 120°C; e) $Hg(CF_3COO)_2$, $EtOCHCH_2$, RT

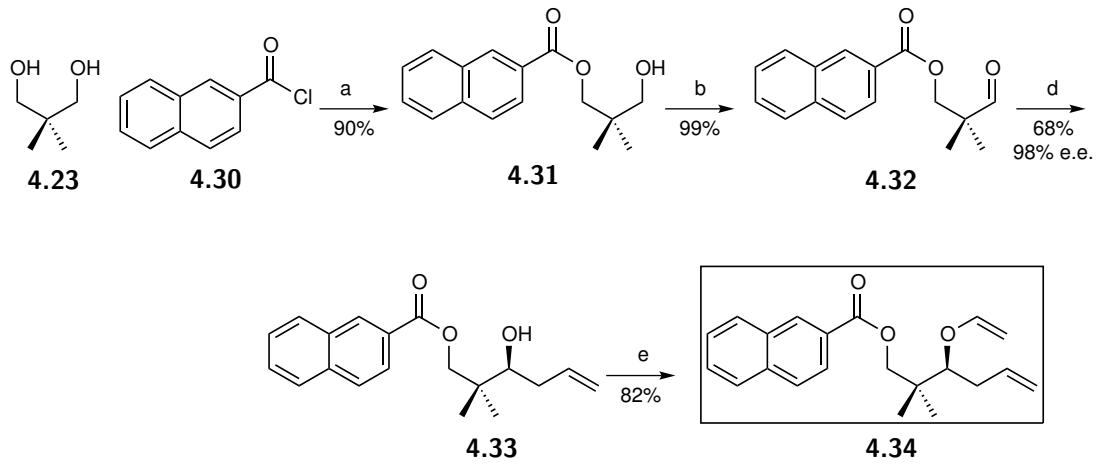
Scheme 4.4: Synthesis of enol ether **4.28**

The other building block (**4.28**), necessary for the synthesis of fragment **4.5**, started with the acetalisation of 2,2-dimethyl-1,3-propanediol with 4-methoxybenzyl dimethylacetal, followed by reductive opening to alcohol **4.25** (scheme 4.4). This was oxidized under Swern conditions, delivering aldehyde **4.26**, which was stereoselectively allylated with a chiral iridium catalyst, at elevated temperatures. The resulting homoallylic alcohol **4.27** was vinylated using mercury catalysis to form bisnucleophile **4.28**. The overall yield for this building block was 62% over 5 steps and the enantiomeric excess 96%.



Scheme 4.5: First attempt on the Mukaiyama aldol - Prins cyclization

In a first attempt to perform the Mukaiyama aldol - Prins cyclization between aldehyde **4.6** and diene **4.28**, the *p*-methoxybenzyl ether proved not to be compatible with the Lewis acidic conditions required for the cyclization (scheme 4.5). As a consequence, only acetal **4.29** was formed. Therefore, the diene was resynthesized using a less sensitive ester as protecting group.



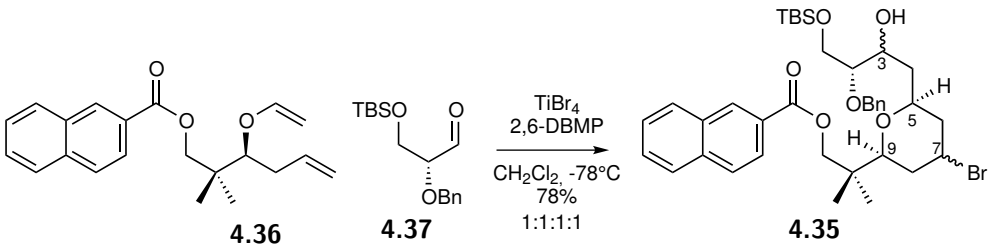
a) DMAP, NEt_3, CH_2Cl_2, RT; b) [i] $(COCl)_2$, DMSO, -78°C [ii] Et_3N, CH_2Cl_2, -78°C; c) $[Ir(cod)Cl]_2$, (*S*)-(-)-Cl, MeO-BIPHEP, Cs_2CO_3, 4-Cl-3-NO_2-benzoic acid, THF, allylOAc, 120°C; d) $[Ir(cod)Cl]_2$, (*S*)-(-)-Cl, MeO-BIPHEP, Cs_2CO_3, 4-Cl-3-NO_2-benzoic acid, THF, allylOAc, 2-PrOH, 120°C; e) $Hg(CF_3COO)_2$, $EtOCHCH_2$, RT

Scheme 4.6: Synthesis of the ester protected C_4-C_{11} enol ether **4.34**

The synthesis of the naphtoyl-protected enol ether started with the monoprotection of diol **4.23** with naphtoylchloride (scheme 4.6). Swern oxidation of the remaining alcohol in **4.31** yielded aldehyde **4.32** which could be allylated under Krische conditions, affording homoallylic alcohol **4.33** in an isolated yield of 68%

with an enantiomeric excess of 98%. The final mercury-catalyzed vinylation occurred with a yield of 82%. Overall, this 2nd generation enol ether was synthesized in 4 steps with a total yield of 50% with an excellent enantiopurity.

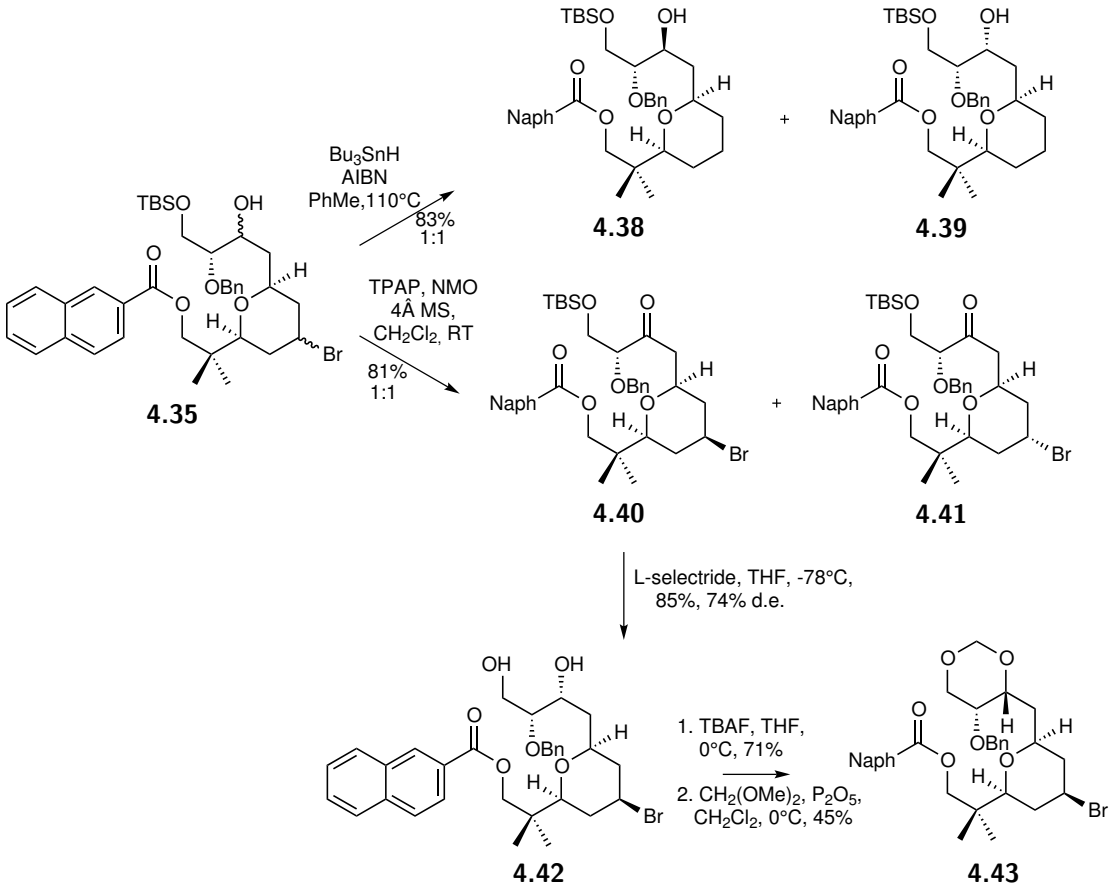
The second attempt on the Mukaiyama aldol - Prins cyclization, was successful in terms of carbon-skeleton formation, but not in terms of stereoselectivty: the envisaged bromo-THP ether **4.35** was formed in 78% yield, be it as a mixture of diastereomers at the bromine center and the C_3 alcohol (scheme 4.7). Attempts to improve the diastereoselectivity by changing the Lewis acid, the order of addition or control of the temperature all failed. Increasing the bulk of the aldehyde by replacement of the TBS ether by a less acid sensitive TBDPS ether improved the yield of the cascade reaction to 84%, without improving the diastereomeric outcome.



Scheme 4.7: Mukaiyama aldol - Prins cyclization with enol ether **4.36**

The complex mixture was analyzed by means of chemical derivatization (scheme 4.8): reductive removal of bromine gave the two diastereomeric alcohols at C_3 (**4.38** and **4.39**), whereas oxidation of this C_3 alcohol to the ketone, gave both equatorial **4.40** and equatorial bromide **4.41**. The stereocenter at C_5 was always *cis* compared to the substituent at C_9, the latter which was established previously in the allylation reaction.

After separation, ketone **4.40** was stereoselectively reduced with L-selectride to alcohol **4.42** in 85% yield, now enriched in one diastereomer. The configuration of this alcohol was established by deprotecting the TBS ether and forming acetal **4.43** between the alcohols at C_1 and C_3. From the Karplus relation, it could be derived that the newly formed hydroxyl is in *syn* position compared to the benzyloxy



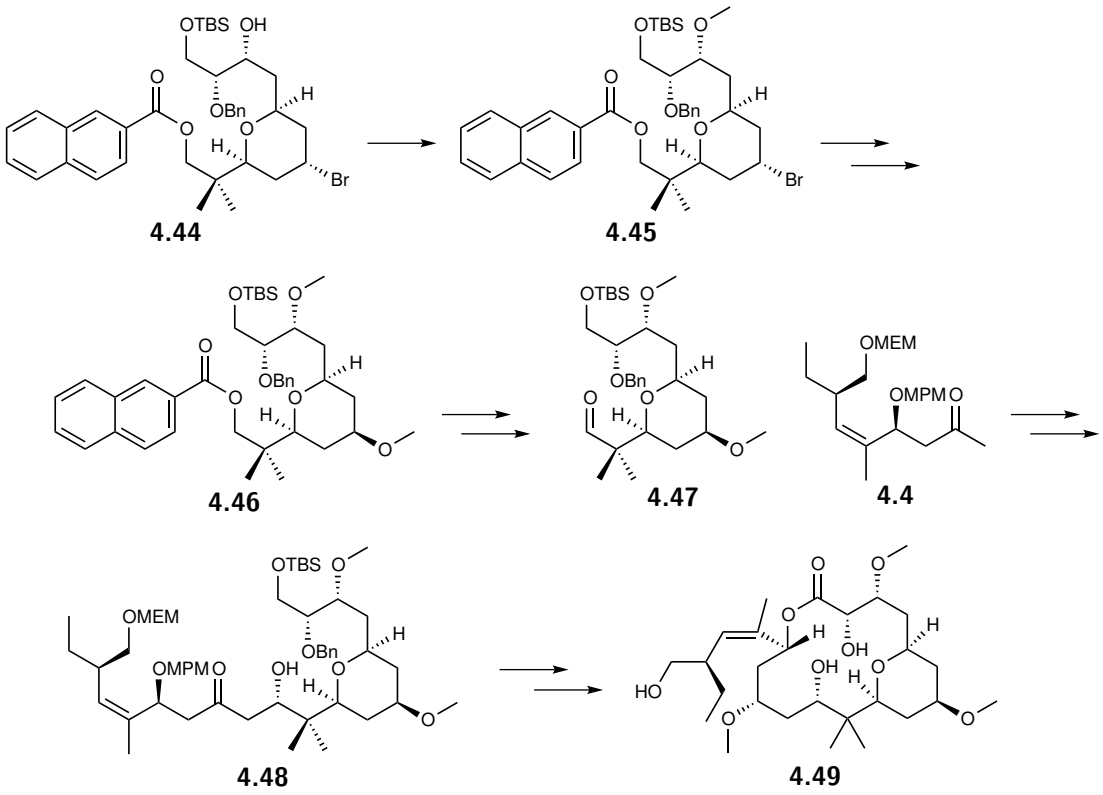
Scheme 4.8: Derivatization and further elaboration of the MAP-product **4.35**

group, originating from the chiral pool. Thus, the correct stereochemistry was installed.

4.2.2 Future perspectives

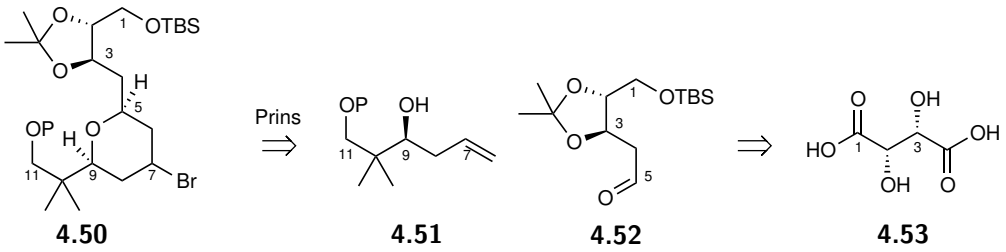
Important steps in the further elaboration of the C_1-C_{11} fragment (scheme 4.9) include methylation of the C_3-alcohol of **4.44**, and transformation of the resulting bromide **4.45** to , for instance, methyl ether **4.46**. After deprotection of the naphtoyl ester, the primary alcohol should be oxidized to aldehyde **4.47**, which can then be coupled with the $C_{12}-C_{20}$ fragment **4.4** in an aldol coupling, resulting in **4.48**. After this, one more stereoselective (reductive) step is needed to complete

the full carbon skeleton with the correct stereochemistry. Deprotection and oxidation are then key to form the ω-hydroxy acid, necessary for macrolactonization. Final deprotection would then give the 8,9-dehydroxy analog **4.49** of peloruside.



Scheme 4.9: Future steps for the completion of the synthesis of the 8,9-dehydroxy analog of (+)-Peloruside A.

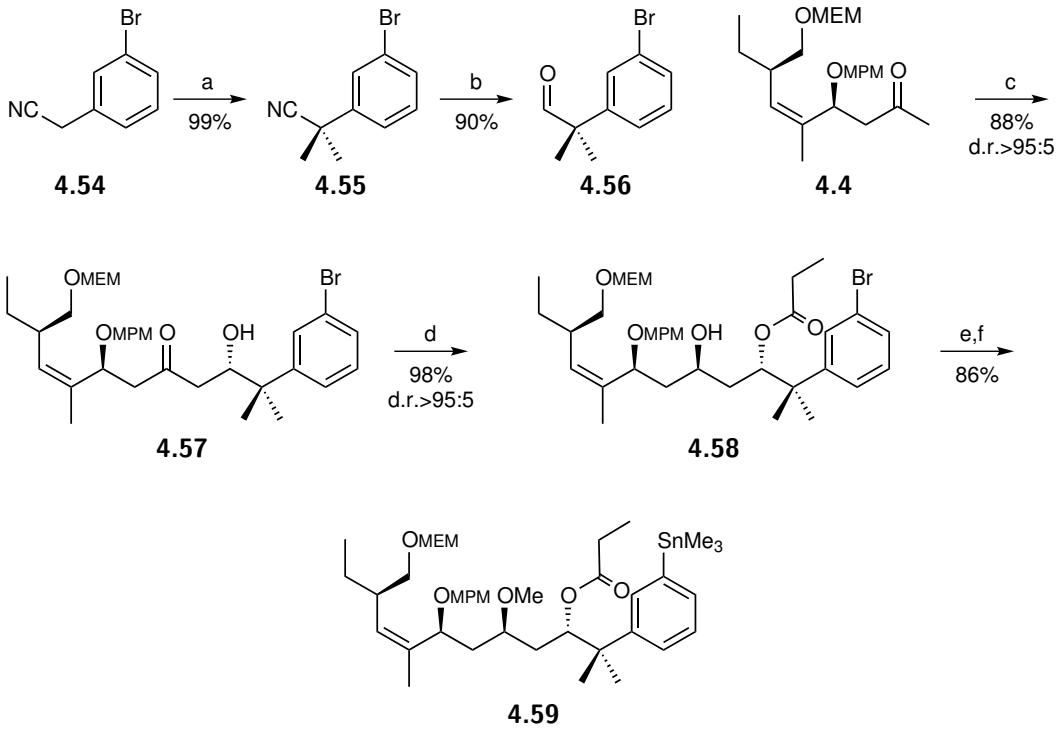
In light of the difficulties encountered with the installation of the correct stereochemistry in **4.44**, using the Mukaiyama aldol-Prins approach, an alternative approach might be more successful. As described in scheme 4.10, the tetrahydropyranyl group in **4.50** could be constructed from reaction of homoallylic alcohol **4.51** with aldehyde **4.52** in a classic Prins reaction.[203] The aldehyde itself can be constructed from D-(-)-tartaric acid (**4.53**), a chiral compound which already posseses the desired stereochemistry. This synthesis is described in literature.[204,205]



Scheme 4.10: Alternative build-up for the tetrahydropyranyl ring.

4.3 Phenyl analogs

4.3.1 Improved synthesis of pelofen B *via* macrolactonization



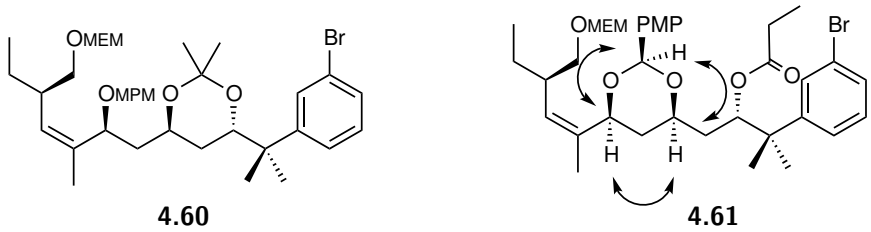
a) KO*t*Bu, MeI, THF, -40°C; b) [i] DIBAH, PhMe, -78°C, [ii] aq. 6M HCl, RT; c) [i] $(Cy)_2BCl$, NEt_3, Et_2O, -78°C; [ii] MeOH, pH 7 buffer, H_2O_2, RT; d) EtCHO, SmI_2, THF, -20°C; e) Me_3OBF_4, 1,8-bis(dimethylamino)naphtalene, CH_2Cl_2, RT; f) $Me_3SnSnMe_3$, $Pd(PPh_3)_4$, PPh_3, PhMe, 70°C

Scheme 4.11: Synthesis of the C_5-C_{20} fragment **4.59** for the synthesis of pelofen

An improved synthesis was developed for pelofen B (**4.3**), starting from the commercially available 3-bromophenyl acetonitrile **4.54**, which was first alkylated to **4.55** (scheme 4.11). This was reduced to the imine, which, after acid hydrolysis, afforded aldehyde **4.56**, in 89% yield over 2 steps. This was coupled with the earlier synthesized $C_{12}-C_{20}$ methyl ketone **4.4** in a stereoselective aldol coupling making use of chlorodicyclohexylborane, delivering β-hydroxyketone **4.57** in 88% yield, as a single diastereomer.

At this stage, the stereochemistry was assigned by the synthesis of the corresponding Mosher esters. Next, Evans-Tishchenko reduction using propionaldehyde and diiodosamarium resulted in the differentiated *anti*-1,3-monoester **4.58**. At this stage, the relative stereochemistry between the alcohol generated in the aldol addition (C_{11}) and the alcohol generated in the Evans-Tishchenko reduction (C_{13}) was established by the synthesis of acetonide **4.60** (figure 4.2), followed by NMR-analysis.

Also, the relative stereochemistry between the MPM protected alcohol (C_{15}) and the alcohol originating from the reduction (C_{13}) was established by synthesis of the corresponding PMP acetal **4.61** (figure 4.2) and NMR analysis. After methylation of the newly formed alcohol in **4.58**, the bromide was converted to trimethyltin-derivative **4.59** in a Pd(0)-catalyzed Stille coupling.

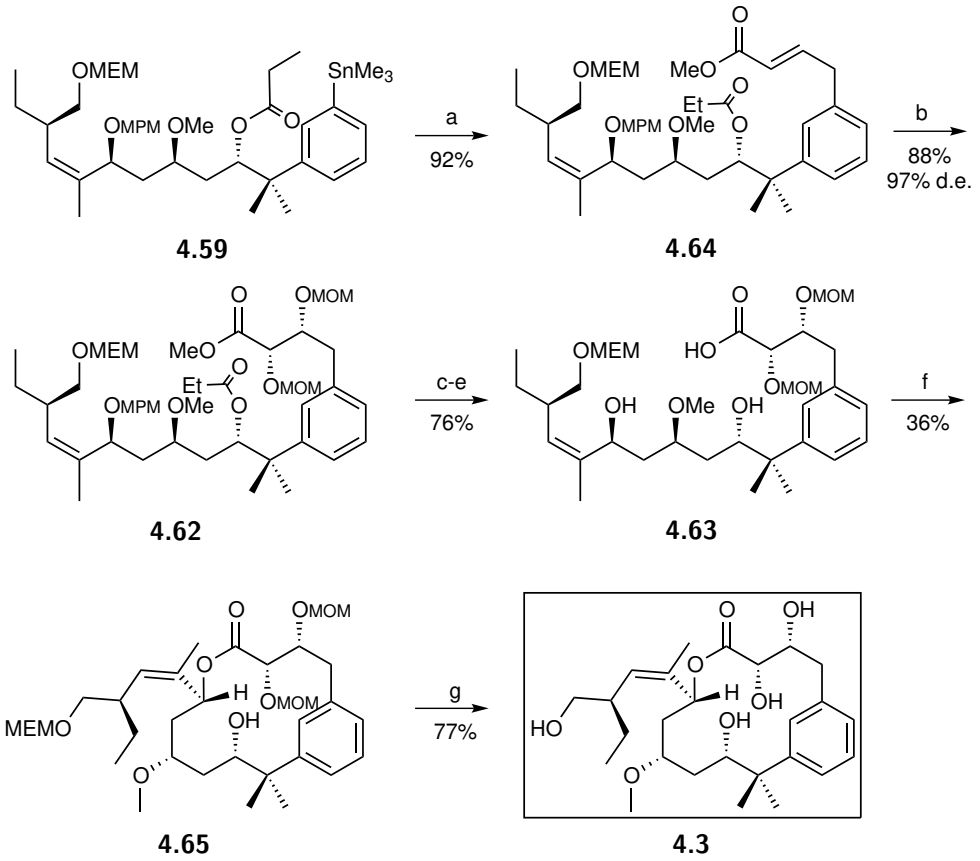


4.60 **4.61**

Figure 4.2

Completion of the carbon skeleton of the phenyl analog **4.3** was achieved by coupling of the advanced stannane **4.59** with commercially available methyl 4-bromocrotonate in a second Stille coupling (scheme 4.12). Dihydroxylation of the resulting double bond was achieved using Sharpless's AD mix β, a combination of a

catalytic amount of $K_2OsO_4 \cdot 2\,H_2O$, a chiral ligand (bis(dihydroquinidine)phtalazine, $(DHQD)_2PHAL$) , a base (K_2CO_3) and a co-oxidant. This afforded diol **4.62** in 88% with a d.e. of 97%. Both alcohols were protected as MOM ethers in 97% yield. The MPM ether was deprotected with DDQ (95% yield), after which both esters were hydrolyzed under basic conditions. LiOH gave the cleanest reaction, but complete conversion took quite long (multiple days). In the end, the ω-hydroxy acid necessary for macrolactonization **4.63** was obtained in 83% after 7 days.



a) (*E*)-4-Br-$CH_2CHCHCOOMe$, $Pd_2dba_3.CHCl_3$, THF, 70°C; b) AD-mix β, $MeSO_2NH_2$, $NaHCO_3$, *t*BuOH:H_2O 1:1, RT; c) MOM-Cl, DIPEA, CH_2Cl_2, reflux; d) DDQ, pH7 buffer, CH_2Cl_2, RT; e) LiOH.H_2O, THF:H_2O 3:1, RT; f) [i] 2,4,6-trichlorobenzoylchloride, DIPEA, THF, RT; [ii] DMAP, PhMe, RT; g) 4M HCl, THF:H_2O 1:1, RT

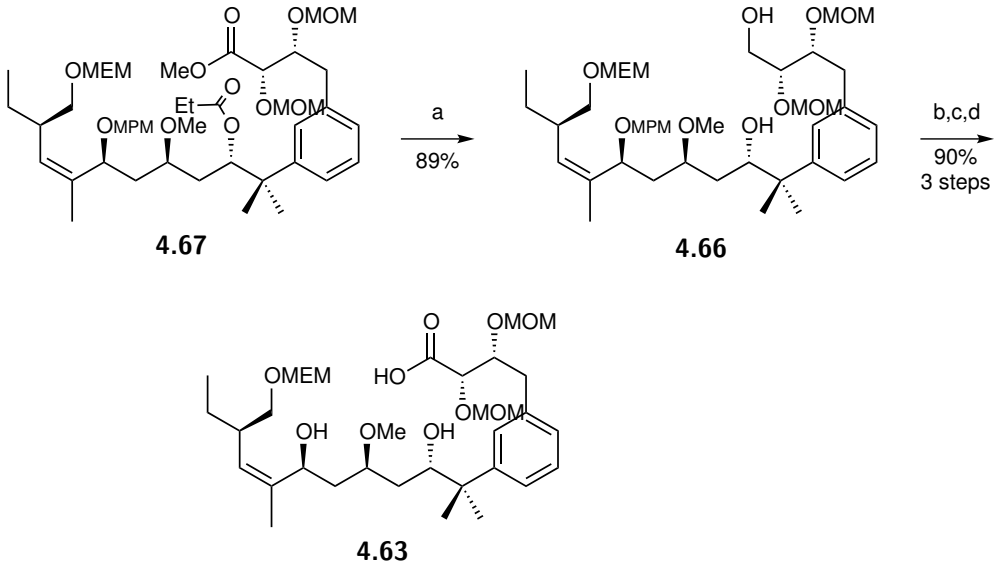
Scheme 4.12: Completion of the synthesis of pelofen **4.3**

To circumvent these longer reaction times, another approach was implemented, where both esters were reduced using $LiALH_4$, with the MPM ether still intact

(scheme 4.13). The resulting primary alcohol **4.66** was then selectively oxidized to the carboxylic acid in two steps. Finally, the MPM ether was successfully cleaved in the presence of the carboxylic acid, affording **4.63** with a combined yield of 80% over four steps.

Different attempts on the macrolactonization were made, but the original yield of 36%, achieved using Yamaguchi conditions could not be improved. Both varying the conditions using 2,4,6-trichlorobenzoylchloride or trying a number of different activating agents were insufficient in improving the yield. The final deprotection under acidic conditions, resulted in the desired phenyl analog **4.3** in 77% yield.

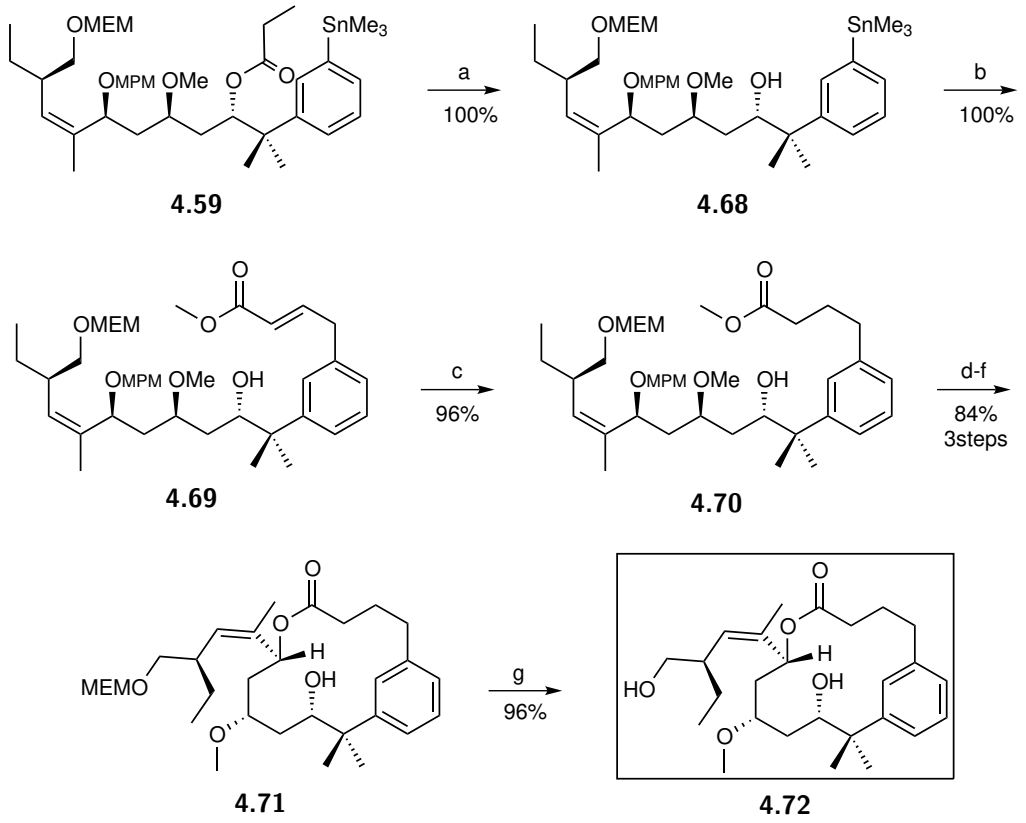
Overall, the synthesis was completed in a longest linear sequence of 20 steps, starting from ethylmagnesium chloride, the total number of steps being 22, resulting in an overall yield of 2.7%. This represents an improvement of the original route by 1 step in longest linear sequence, 4 steps in the total number of steps and an improved yield by almost 400% (0.7% overall yield in the original route).



a) $LiAlH_4$, Et_2O, 0°C; b) TEMPO, $PhI(OAc)_2$, CH_2Cl_2,RT; c) NaH_2PO_4, $NaClO_2$, 2-Me-2-butene, tBuOH:H_2O 1:1, RT; d) DDQ, pH 7 buffer, CH_2Cl_2, RT

Scheme 4.13: Alternative synthesis of the *seco* acid **4.63**.

4.3.2 Synthesis of 2,3-dideoxy pelofen (3.74)



a) $LiAlH_4$, Et_2O, 0°C; b) (*E*)-4-Br-$CH_2CHCHCOOMe$, $Pd_2dba_3.CHCl_3$, THF, 70°C; c) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, 0°C; d) DDQ, pH7 buffer, CH_2Cl_2, RT; e) $LiOH.H_2O$ THF:H_2O 1:1 RT; f) [i] 2,4,6-trichlorobenzoylchloride, DIPEA, PhMe, RT; [ii] DMAP, PhMe, RT; g) *n*-BuSH, $ZnBr_2$, CH_2Cl_2, RT

Scheme 4.14: Synthesis of the 2,3-dideoxy analog of pelofen (**4.72**).

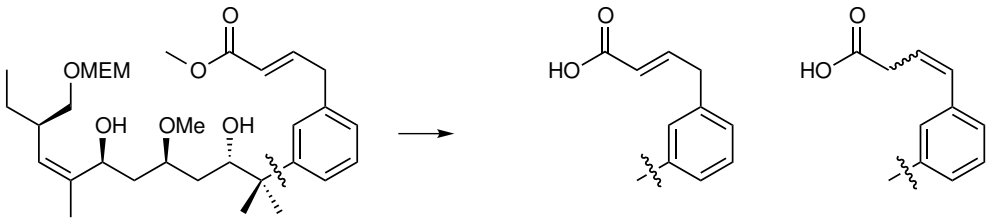
An analog of pelofen B, lacking the C_2 and C_3 substituents, could give insight in the importance of these hydroxyl groups for the activity. This analog was easily accessible through the previously developed route (scheme 4.14).

Starting from stannane **4.59** we anticipated the difficult deprotection of the propionate ester, so it was reduced first. The resulting alcohol **4.68** could be used without protecting group in the following steps. Stille coupling with the earlier used methyl 4-bromocrotonate resulted in unsaturated ester **4.69**. The double bond of this conjugated ester was reduced with $NaBH_4$ under nickel catalysis,

without affecting the double bond present in the side chain, delivering ester **4.70** in 96% yield over three steps. The *seco*-acid necessary for macrolactonization was generated by deprotection of the MPM-ether and consecutive basic hydrolysis of the methyl ester. The macrolactonization, applying Yamaguchi conditions, this time delivered the macrolactone **4.71** in a high yield (84% over three steps). The final deprotection using a Lewis acid in combination with a thiol as a scavenger, proceeded extremely well, affording the 2,3-dideoxy analog of pelofen **4.72** in 96% yield.

Overall, the synthesis of this analog was accomplished in 20 steps, starting from ethylmagnesium chloride, with a total number of 22 steps and a total yield of 12%. So far, no statistically significant results for the activity of this analog are available.

4.3.3 New route to pelofen B and analogs at the C_2-C_3-position



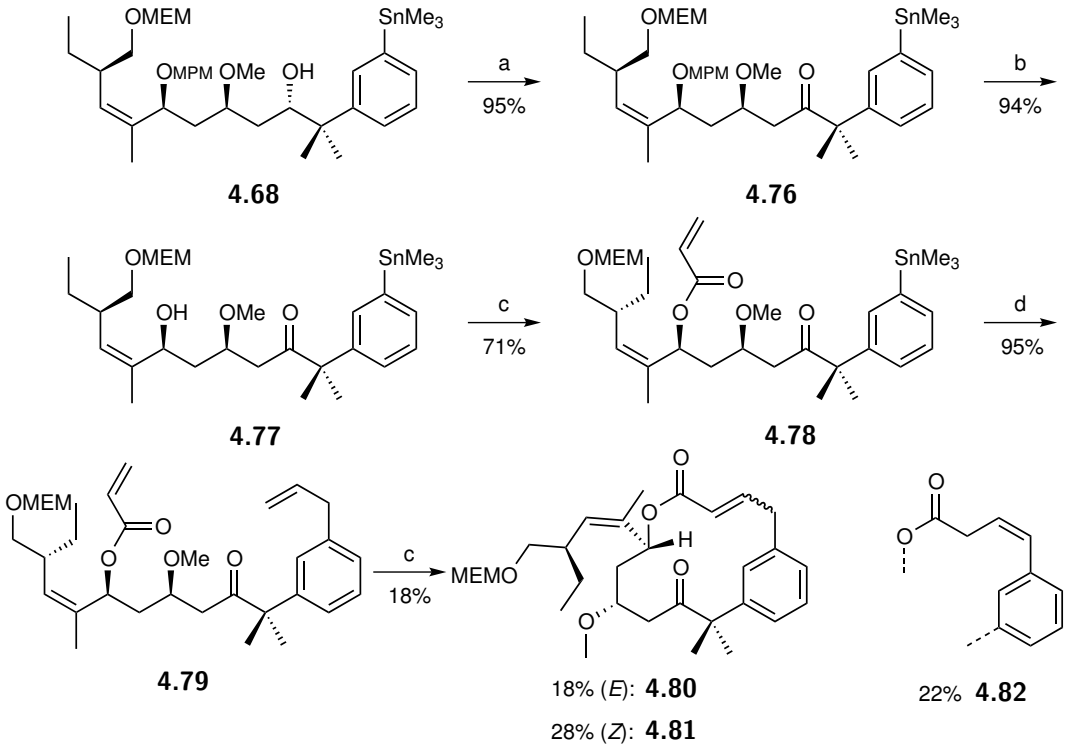
4.73 **4.74** **4.75**

Scheme 4.15: Observed isomerization in the saponification of **4.73**

As the macrolactonization of the unsubstituted analog proceeded very smoothly, attempts were made to perform the ring closure while the double bond at C_2-C_3 was still present. This approach would have provided rapid access to analogs in this region, as substituents could be introduced at a very late stage in the synthesis, after macrocyclization and maybe even after final deprotection. Unfortunately, upon saponification of the conjugated methyl ester **4.73**, a minor amount of the envisaged carboxylic acid **4.74** was formed, and isomerization of the double

bond towards the styrene derivatives (**4.75**) was observed (scheme 4.15). Direct Stille coupling of 4-bromocrotonic acid, appeared to be a solution to this problem. However, the same isomerization occurred under the basic conditions used for the macrolactonization. Because of the complexity of the formed reaction mixtures, this route was abandoned.

4.3.4 Pelofen B *via* ring-closing metathesis



a) TPAP, NMO, 4Â molecular sieves, CH_2Cl_2,RT; b) DDQ, pH7 buffer, CH_2Cl_2, 0°C; c) $CH_2CHCOCl$, DIPEA, CH_2Cl_2, RT, 0°C; d) CH_2CHCH_2Br, $Pd_2dba_3.CHCl_3$, 60°C; e) Grubbs II, PhMe, 110°C

Scheme 4.16: Synthesis of unsaturated macrolactone **4.80** through ring-closing metathesis

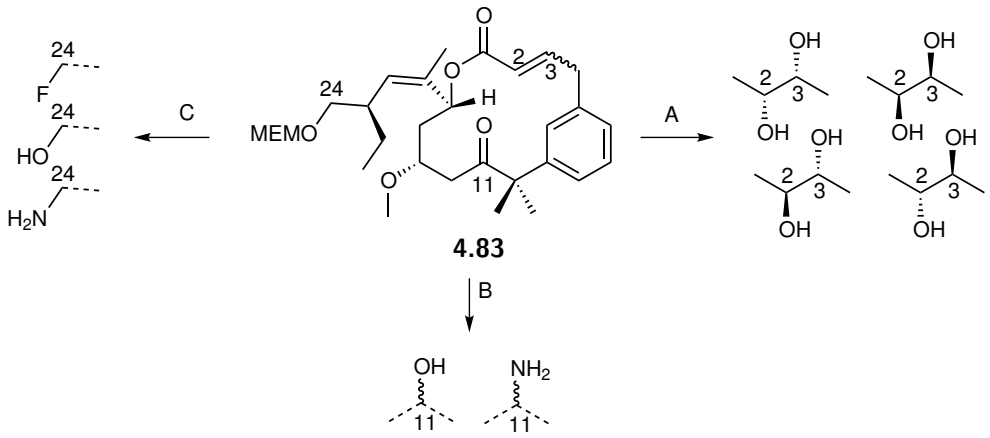
Finally, a last approach to get to pelofen B was tested, based on the ring-closing metathesis reaction (scheme 4.16), which is, besides the macrolactonization, a frequently used reaction in the total synthesis of macrocycles.

It was decided to oxidize the alcohol at the C_{11} position in **4.68** (scheme 4.16), before liberating the allylic alcohol, as selective acrylation proved problematic. This way of 'protecting' the alcohol at C_{11} could later on give access to the envisaged alcohol as well as the inverted one, and also introduction of other substituents were thought to be possible. The oxidation was achieved using ruthenium catalysis and delivered ketone **4.76** in 95% yield. Next, the MPM ether was removed, liberating allylic alcohol **4.77**. The optimized conditions for the acryloylation, employing a 0.1M solution of acryloyl chloride in CH_2Cl_2 and DIPEA resulted in acryloyl ester **4.78** in 71%, with still some 10% starting alcohol left. The final step in the formation of the precursor diene **4.79** was the allylation reaction of the aromatic ring under Stille conditions, which occurred in neat allyl bromide, with a yield of 95%, without notable isomerization of the double bond. The metathesis reaction itself was optimized in terms of monomer versus oligomer formation in function of dilution, solvent, catalyst, reaction time, and temperature. Employing Grubbs' 2 nd generation catalyst at 110°C in toluene for short reaction times, the reaction reached an optimal ratio of 70:30, in favor of the monomer. It was expected that a mixture of the *E* and *Z* double bond would be formed. During the scale up of this reaction, however, it was observed that the 66% isolated ring closed product was comprised of a mixture of the *Z* and *E* isomer **4.80** of the ring-closed conjugated ester (28% vs. 18%, respectively) as well as of the *Z*-styrene derivative (22%).

4.3.5 Future perspectives

During this work, the synthesis of pelofen B itself was optimized for all but one steps, being the macrolactonization. A parameter that was not investigated during this macrolactonization is the influence of the temperature. In light of the good results of the ring closing metathesis at higher temperatures, this could be a viable option for the further optimization of this reaction.

For the fast introduction of modifications at a later stage in the synthesis (scheme 4.17), the ring closing metathesis approach seems the better choice. Start-



Scheme 4.17: Rapid access to pelofen analogs through diversification of **4.83**

ing from the unsaturated macrocycle **4.83**, different analogs can be accessed in a simple way (scheme 4.17). At the C_2-C_3 position, dihydroxylation of the *E*-double bond should result in the *syn* alcohols, whereas dihydroxylation of the *Z*-olefin should result in the *anti* diols (step A). Reduction of the ketone at C_{11} will give both epimeric alcohols, whereas reductive amination would give the epimeric amines (step B). The primary alcohol at C_{24} can be easily deprotected under acidic conditions, so it will be prone to substitution reactions (step C).

5

Experimental procedures

5.1 General info

All reactions were carried out under an argon atmosphere in oven-dried glassware, and solvents were freshly distilled prior to use, except if otherwise indicated. Diethyl ether and tetrahydrofuran were distilled from sodium/benzophenone, toluene and benzene from sodium. Dichloromethane, 2,6-lutidine, pyridine and trietylamine were distilled from calcium hydride.

Reactions were monitored by thin layer chromatography (TLC) on 0.25mm Macherey-Nagel SIL G-25 UV254 silica gel plates. Visualization occurred by UV-light (254 nm) and by staining in a molybdate solution (0.4 g $Ce(SO_4)_2$, 10 g $(NH_4)_6Mo_7O_{24}.4H_2O$, 200 ml H_2O and 10 ml conc. H_2SO_4) or in a permanganate solution (3 g $KMnO_4$, 20 g K_2CO_3, 5 ml 5% aqueous NaOH and 300 ml H_2O). Flash chromatography was carried out with silica gel supplied from Davisil (30-200 μm) or Rocc (40-63 μm) for more difficult separations using solvents of technical quality. All other reagents were purchased from Aldrich, Acros or TCI and used without purification, unless noted otherwise.

^{1}H NMR- and ^{13}C NMR-spectra were recorded on a Bruker Avance 300 or a Bruker AM 500 spectrometer as indicated, with chemical shifts (δ) reported in ppm relative to the residual solvent signal of the deuterated solvent. Multiplicities are reported as singlet (s), doublet (d), triplet (t) and quartet (q) or combinations thereof, while coupling constants (J) are reported in Hz. When necessary, multiplets were analyzed using Gaussian fitting parameters, instead of the standard exponential parameters. ^{13}C NMR-spectra were recorded using the attached proton test (APT).

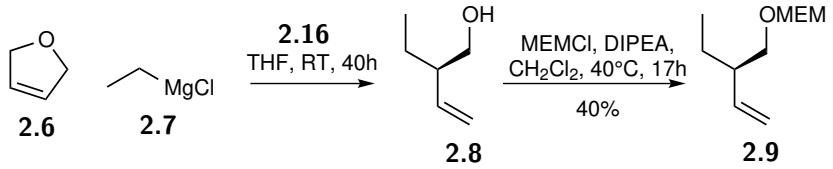
IR-spectra were recorded on a Perkin-Elmer SPECTRUM 1000 FT-IR spectrometer with a Pike Miracle HATR module unless otherwise indicated. Optical rotation was recorded with a Perkin-Elmer 241 polarimeter at 589 nm and/or 365 nm. Melting points were recorded with an Electrothermal IA 9100 series.

EI-MS were recorded on a Hewlett-Packard 5989A mass spectrometer or a Hewlett-Packard G1800B GCD system. LCMS and MS analysis were performed on an Agilent 1100 series HPLC system with a diode array detector and single quad

MS detector (G1946C) with an electrospray ionization source (ESI-MS), using a Phenomenex Luna C18(2) column (250 x 4.6 mm; 5 μm) or Phenomenex Kinetex C18 column (150 x 4.6 mm; 5 μm). HRMS spectra were recorded with an Agilent 6220A time-of-flight MS detector with a multimode ionization source. Analytical chiral LC separation was performed with an Agilent 1100 series HPLC system with a diode array detector, using a Chiralcel (OD-H, OJ-H, OB-H) or Chiralpak (AD-H, AS-H, IA) column.

5.2 Synthesis of the $C_{12}-C_{20}$ fragment 2.2

5.2.1 Synthesis of MEM-protected homoallylic alcohol 2.9



To a solution of 2,5-dihydrofuran (**2.6**) (3.92 ml, 51.8 mmol, 1.33 eq.) in THF (16 ml) at 0°C was added ethylmagnesium chloride (**2.7**) (19.5 ml of 2.0M solution in THF, 38.9 mmol, 1 eq.) dropwise. The mixture was warmed to RT and stirred for an additional 15 min. The contents of an unopened flask of (*S,S*)-ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)zirconium (*R*)-1,1'-bi-2-naphtholate (**2.16**, 133 mg, 0.156 mmol, 0.5 mol%) were added entirely and the reaction flask was shielded from light. After stirring for 40h, the reaction was quenched by pouring in a saturated aqueous solution of NH_4Cl (100 ml), extracted with Et_2O (3 x 100 ml). The combined organic fractions were dried over $MgSO_4$ and concentrated through atmospheric destillation (vigreux). The crude product (**2.8**) was dissolved in CH_2Cl_2 (11.7 ml) and DIPEA (8.14 ml, 64.7 mmol, 1.2 eq.) was added. Upon dropwise addition of MEM-Cl (4.45 ml, 38.9 mmol, 1 eq.) formation of a white fume was observed. The solution was refluxed for 17 h and afterwards poured in a saturated aqueous solution of $NaHCO_3$ (20 ml). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 20 ml). After drying over $MgSO_4$

the solvent was removed by careful evaporation *in vacuo*. Flash chromatography (CH_2Cl_2/Et_2O 98/2) provided **2.9** (2.94 g, 40% yield) as a pale yellow, clear oil.

Name: (*R*)-3-(((2'-methoxyethoxy)methoxy)methyl) pent-1-ene

Formula: $C_{10}H_{20}O_3$

Molecular weight: 188.3 g/mol

R_f: 0.38 (pentane/ Et_2O 7/3)

$[\alpha]_D$ = -15.9 (c = 0.97 in $CHCl_3$)

$[\alpha]_{365}$ = -52.2 (c = 0.97 in $CHCl_3$)

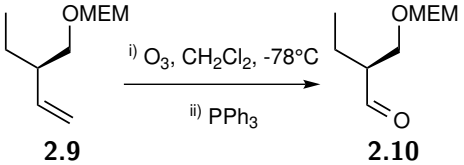
^{1}H-NMR (300 MHz; C_6D_6): δ (ppm) = 5.71-5.59 (1H, m), 5.08-5.02 (2H, m (app. d)), 4.59 (2H, s), 3.62-3.59 (2H, m (app. t)), 3.49-3.37 (2H, m), 3.34 (2H, t, J = 4.7 Hz), 3.12 (3H, s), 2.24-2.13 (1H, m), 1.62-1.48 (1H, m), 1.34-1.19 (1H, m), 0.87 (3H, app. t, J = 7.4 Hz)

APT (75 MHz; C_6D_6): δ (ppm) = 140,88 (CH); 115,91 (CH_2); 96,11 (CH_2); 72,52 (CH_2); 71,50 (CH_2); 67,50 (CH_2); 59,20 (CH_3); 46,15 (CH); 24,69 (CH_2); 11,94 (CH_3)

IR (HATR): 3733 (w), 3080 (w), 2960, 2926, 2875, 2815, 2355, 2337, 2210 (w), 2057 (w), 1640, 1457, 1420, 1380, 1365, 1284, 1242, 1200, 1178, 1157, 1113, 1098, 1047 (s), 1023, 994, 950, 913, 849, 768, 678 cm^{-1}

EI-MS (m/z; (%)): 119 (2), 113 (6), 105 (1), 95 (3), 90 (5), 89 (100), 84 (2), 83 (8), 82 (15), 77 (1), 73 (2), 71 (3), 69 (3), 68 (1), 67 (4), 60 (3), 59 (59), 57 (2), 56 (1), 55 (15), 54 (2), 53 (2), 45 (6), 44 (3), 43 (4), 42 (1), 41 (8)

5.2.2 Synthesis of aldehyde 2.10



2.9 **2.10**

Through a solution of **2.9** (7.53 g, 40 mmol, 1 eq.) in CH_2Cl_2 (40 ml) at -78°C was bubbled ozone until the reaction mixture colored blue. After an additional 20 min of bubbling ozone, the excess O_3 was removed by bubbling Ar through the solution until the blue color disappeared. A solution of PPh_3 (12.59 g, 48 mmol, 1.2 eq.) in CH_2Cl_2 (8 ml) was added *via* a double-ended needle and the flask was rinsed with CH_2Cl_2 (4 ml) after which the temperature was raised slowly to RT and concentrated carefully *in vacuo*. Purification by means of flash chromatography (pentane/Et_2O 6/4) provided pure **2.10** (7.16 g), which was not completely dried due to its volatility, and used as such in the next reaction.

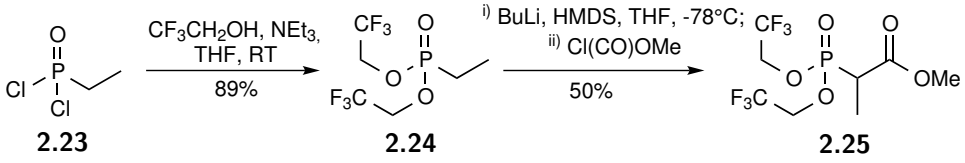
Name: (*S*)-2-(2'-methoxyethoxymethyl)-butanal

Formula: $C_9H_{18}O_4$

Molecular weight: 190.2 g/mol

R_f: 0.16 (pentane/ Et_2O 6/4)

5.2.3 Synthesis of phosphonate 2.25



2.23 **2.24** **2.25**

Synthesis of phosphonate ester 2.24

To a solution of $CF_3CH_2CH_2OH$ (29.3 ml, 408 mmol, 2 eq.) in THF (610 ml) at 0°C, was added NEt_3 (62.6 ml, 449 mmol, 2.2 eq.), followed by a solution of ethylphosphonic dichloride (**2.23**) (21.8 ml, 204 mmol, 1 eq.) in THF (80 ml) with formation of white fume and white precipitate. The addition funnel was rinsed with THF (22 ml) and the reaction mixture was warmed to RT and stirred for 2h. The slightly brown solution with white precipitate was filtered over celite and rinsed with dry THF. The solvent was removed through atmospheric destillation

(vigreux). Purification by destillation *in vacuo* provided **2.24** (47.33 g, 84% yield, bp 84°C at 16mm Hg) as a colorless, clear oil.

Name: Ethylphosphonic acid bis-(2',2',2'-trifluoroethyl) ester

Formula: $C_6H_9F_6O_3P$

Molecular weight: 274.1 g/mol

R_f: 0.23 ((hexane/ acetone 8/2))

ESI-MS (m/z): 275.0 ($M + H^+$)

^{1}H-NMR (300 MHz; $CDCl_3$): δ (ppm) = 4.47-4.26 (4H, m), 1.98-1.84 (2H, m), 1.20 (3H, dt, J = 21.6 Hz (^{31}P-^{1}H), 7.7 Hz)

APT (75 MHz;C_6D_6): δ (ppm) = 122,77 (C, dq, J = 275.8 Hz (^{19}F-^{13}C), 7.6 Hz (^{31}P-^{13}C)), 62.03 (CH_2, dq, J = 37.6 Hz (^{19}F-^{13}C), 6.1 Hz (^{31}P-^{13}C)), 19.11 (CH_2, d, J = 142.6 Hz (^{31}P-^{13}C)), 6.02 (CH_3, d, J = 7.1 Hz (^{31}P-^{13}C))

IR (HATR): 1418 (w), 1284, 1252, 1231, 1162 (s), 1106, 1073 (s), 1035, 1015, 961, 841, 731 cm^{-1}

Synthesis of phosphonate 2.25

To *n*-BuLi (200 ml, 1.6M in hexane, 2.1 eq.) at -20°C was added dropwise a solution of HMDS (76.7 ml, 350 mmol, 2.3 eq.) in THF (175 ml). The addition funnel was rinsed with THF (52 ml) and the reaction mixture was stirred for 15' at -20°C. Afterwards, the reaction mixture was further cooled to -78°C, and a solution of **2.24** (41.8 g, 152 mmol, 1eq.) and methyl chloroformate (12.4 ml, 160 mmol, 1.05 eq.) in THF (500 ml) was added dropwise and the addition funnel rinsed with THF (33 ml). The mixture was warmed to 0°C over 45' and diluted aqueous HCl was added, until acidic (control by pH indicator). After separating the organic phase, the aqueous phase was extracted with CH_2Cl_2 (3 x 250 ml) and the combined organic phases were dried over $MgSO_4$ and evaporated *in vacuo*.

Purification by *in vacuo* destillation provided **2.25** (9.09 g, 50% yield, bp 125°C at 16mm Hg) as a colorless, clear oil that solidified on refrigeration.

Name: methyl 2-(bis(2',2',2'-trifluoroethoxy)phosphoryl)propanoate

Formula: $C_8H_{11}F_6O_5P$

Molecular weight: 332.1 g/mol

R_f: 0.31 (hexaan/ethylacetaat 6/4)

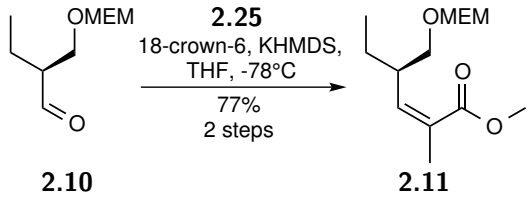
ESI-MS (m/z): 333.0 ($M + H^+$)

^{1}H-NMR (300 MHz; $CDCl_3$): δ (ppm) = 4.50-4.36 (4H, m), 3.78 (3H, s), 3.28-3.13 (1H, m), 1.52 (3H, dd, J = 22.2 Hz (^{31}P-^{1}H), 7.4 Hz)

APT (75 MHz;C_6D_6): δ (ppm) = 169.07 (C, d, J = 3.0 Hz (^{31}P-^{13}C)), 122.60 (C, dq, J = 274.5 Hz (^{19}F-^{13}C), 8.0 Hz (^{31}P-^{13}C)), 62.77 (CH_2, dq, J = 37.8 Hz (^{19}F-^{13}C), 5.9 Hz (^{31}P-^{13}C)), 53.14 (CH_3), 39.50 (CH, d, J = 140.3 Hz (^{31}P-^{13}C)), 11,73 (CH_3, d, J = 6.6 Hz (^{31}P-^{13}C))

IR (HATR): 1740, 1458 (w), 1438 (w), 1420 (w), 1289, 1259, 1162 (s), 1068 (s), 960, 867, 840 cm^{-1}

5.2.4 Synthesis of ester 2.11



2.10 **2.11**

To a solution of **2.25** (15.01 g, 45 mmol, 1.2 eq.), and 18-crown-6 ether (59.72 g, 226 mmol, 6 eq.), in THF (843 ml) at -78°C was added KHMDS (90 ml, 0.5M in toluene, 1.2 eq.) dropwise. After stirring for 20 min at that temperature, a cooled solution of **2.10** (7.16 g) in THF (57 ml) was added. After stirring for

1.5 h, the reaction mixture was poured in a saturated aqueous NH_4Cl solution (700 ml). After separating the organic phase, the water phase was extracted with EtOAc (3 x 700 ml) and the combined organic phases were dried over $MgSO_4$. After evaporation *in vacuo* the mixture was filtered (P4). Purification by flash chromatography (pentane/Et_2O 6/4) provided **2.11** (8.09 g, 77% yield over 2 steps) as a pale yellow, clear oil.

Name: (2*Z*, 4*R*)-Methyl 4-(2'-methoxyethoxymethoxymethyl)-2-methylhex-2-enoate

Formula: $C_{13}H_{24}O_5$

Molecular weight: 260.3 g/mol

R_f: 0.30 (pentane/ Et_2O 6/4)

$[\alpha]_D$ = -32.7 (c = 1.25 in $CHCl_3$)

$[\alpha]_{365}$ = -1.51 (c = 1.25 in $CHCl_3$)

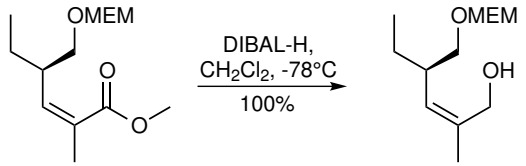
^{1}H-NMR (300 MHz; C_6D_6): δ (ppm) = 5.71 (1H, d, J = 9.8 Hz); 4.60 (2H, s); 3.64-3.58 (3H, m), 3.51 (2H, d, J = 5.6 Hz), 3.37-3.34 (5H, m), 3.13 (3H, s), 1.89 (3H, s), 1.71-1.57 (1H, m), 1.40-1.26 (1H, m), 0;92 (3H, app. t, J = 7.4 Hz)

APT (75 MHz; C_6D_6): δ (ppm) = 167.74 (C), 144.91 (CH), 128.46 (C), 95.54 (CH_2), 72.07 (CH_2), 70.78 (CH_2), 67.06 (CH_2), 58.50 (CH_3), 50.67 (CH_3), 40.86 (CH), 25.11 ((CH_2), 20.95 (CH_3), 11.70 (CH_3)

IR (HATR): 2953, 2929, 2874, 1716 (m), 1647 (w), 1455, 1435, 1366 (w), 1260, 1219 (m), 1192, 1176, 1156, 1132, 1113, 1093 (s), 1045 (s), 1020, 989, 946 (w), 934 (w), 890 (w), 847, 826 (w), 770 cm^{-1}

EI-MS (m/z; (%)): 149 (6), 95 (8), 90 (5), 89 (66), 88 (4), 86 (18), 85 (5), 84 (30), 67 (6), 59 (78), 55 (7), 53 (4), 51 (17), 49 (55), 48 (6), 47 (14), 46 (39), 45 (100), 44 (9), 43 (24), 42 (11), 41 (18)

5.2.5 Synthesis of allylic alcohol 2.12



2.11 **2.12**

To a solution of **2.11** (8.09 g, 31.09 mmol, 1 eq.) in CH_2Cl_2 (311 ml) at -78°C was added DIBAL-H (77.7 ml, 1.0M in hexane, 2.5 eq.)) dropwise. After stirring for 1 h at -78°C, a saturated solution of Rochelle's salt in water (414 ml) was added and the reaction mixture was warmed to RT. After stirring for 3h at RT, the mixture was transferred to a separation funnel, the organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 414 ml). The combined organic phases were dried over $MgSO_4$ and evaporated *in vacuo*. Purification by flash column chromatography (CH_2Cl_2/ acetone 85/15) provided **2.12** (7.20 g, 100% yield) as a pale yellow, clear oil.

Name: ((2*Z*,4*R*)-4-(2'-Methoxyethoxymethoxymethyl)-2-methylhex-2-en-1-ol

Formula: $C_{12}H_{24}O_4$

Molecular weight: 232.3 g/mol

R_f: 0.24 (CH_2Cl_2/ acetone 85/15)

$[\alpha]_D$ = +11.4 (c = 1,25 in $CHCl_3$)

$[\alpha]_{365}$ = +49.7 (c = 1,25 in $CHCl_3$)

ESI-MS (m/z): 255.1 ($M + Na^+$)

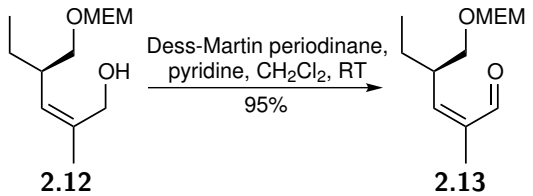
^{1}H-NMR (300 MHz; C_6D_6): δ (ppm) = 4.94 (1H, d, J = 9.9 Hz), 4.49 (2H, s), 4.26 (1H, d, J = 11.6 Hz), 3.87-3.81 (1H, m), 3.54 (2H, t, J = 5.4 Hz), 3.38-3.29 (3H, m), 3.17 (1H, t, J = 9.0 Hz), 3.11 (3H, s), 2.58-2.46 (1H, m), 2.27 (1H, d, J = 5.4 Hz), 1.83 (3H, s), 1.37-1.24 (1H, m), 1.12-0.97 (1H, m), 0.78 (3H, app. t, J = 7.32 Hz)

APT (75 MHz; C_6D_6): δ (ppm) = 138.47 (Cq), 130.24 (CH), 95.57 (CH_2), 72.17 (CH_2), 71.33 (CH_2), 67.33 (CH_2), 61.92 (CH_2), 58.63 (CH_3), 40.26 (CH), 25.25 (CH_2), 22.52 (CH_3), 11.87 (CH_3)

IR (HATR): 3428 (b), 2958, 2923, 2874, 1453, 1412 (w), 1377 (w), 1242 (w), 1199 (w), 1172, 1108 (m), 1043 (s), 1013 (s), 945, 900 (w), 849 cm^{-1}

EI-MS (m/z; (%)): 149 (11), 141 (5), 126 (10), 105 (6), 97 (19), 96 (61), 95 (11), 89 (56), 86 (18), 84 (34), 83 (14), 82 (8), 81 (50), 79 (7), 73 (8), 72 (8), 71 (8), 69 (14), 67 (9), 59 (100), 57 (14); 56 (5); 55 (24); 51 (17); 49 (57); 47 (12); 46 (10); 45 (52); 44 (5); 43 (57); 42 (6); 41 (29)

5.2.6 Synthesis of aldehyde 2.13



To a solution of **2.12** (4.50 g, 19.4 mmol, 1 eq.) in CH_2Cl_2 (193 ml) at 0°C was added pyridine (7.8 ml, 96.9 mmol, 5 eq.) and fresh Dess-Martin periodinane (12.3 g, 29.1 mmol, 1.5 eq.). The reaction mixture was warmed to RT and stirred for 1h before adding a premixed solution of saturated aqueous $Na_2S_2O_3$ (200 ml) and $NaHCO_3$ (200 ml). After 15' of stirring, the mixture was transferred to a separation funnel, the organic phase was separated and the remaining aqueous phase was extracted with EtOAc (3 x 400 ml), dried over $MgSO_4$ and carefully evaporated *in vacuo*. Purification by means of flash chromatography (CH_2Cl_2/ acetone 92/8) provided **2.13** (4.24 g, 95%) as a yellow, clear oil.

Name: ((2*Z*,4*R*)-4-(2'-Methoxyethoxymethoxymethyl)-2-methylhex-2-enal

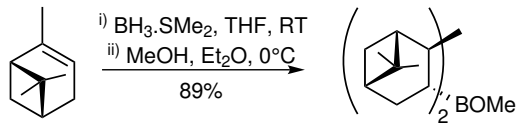
Formula: $C_{12}H_{22}O_4$

Molecular weight: 230.3 g/mol

R_f: 0.47 (CH_2Cl_2/ acetone 93/7)

5.2.7 Synthesis of homoallylic alcohol 2.14

Synthesis of (-)-diisopinocampheylmethoxyborane (2.27)

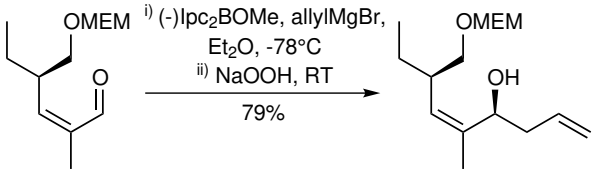


2.26 **2.27**

To a stirring solution of (+)-α-pinene (**2.26**), freshly distilled over CaH_2, (17.7 ml, 112 mmol, 2.5 eq.) in THF (13.4 ml) was added $BH_3 \cdot SMe_2$ (4.2 ml, 45 mmol, 1 eq.) over 30' at a constant temperature of 23°C. After the addition, the stirring was stopped and the solution was left untouched overnight, during which white crystals were formed. The solution was then cooled to 0°C for 2h, after which the supernatans was removed using a double-ended needle. The white chrystals were washed with pre-cooled, dry Et_2O (3 x 8 ml) at 0°C, and dried, first by blowing Ar, then overnight *in vacuo*, yielding (-)-diisopinocampheylborane (11.4 g, 40 mmol, 89%)

(-)-diiospinocampheylborane (11.4 g, 40 mmol, 1 eq.) was suspended in Et_2O (40 ml) and cooled to 0°C. MeOH (1.6 ml, 40 mmol, 1 eq.) was then added dropwise and the solution was stirred at RT until everything was dissolved to form **2.27**.

Allylation



2.13 **2.14**

The solution of (-)-diisopinocampheylmethoxyborane (**2.27**) (12.6 g, 40 mmol, 2.4 eq) in Et_2O (40 ml) was diluted with Et_2O (143 ml) and cooled to -78°C. Allylmagnesiumbromide (40 ml, 40 mmol, 1M in Et_2O, 2.4 eq.) was added dropwise, upon which the reaction mixture became turbid and a black aggregate was formed. The reaction mixture was first stirred for 15' at -78°C, followed by 1h of stirring at RT, resulting in a white solution. The reaction mixture was then cooled back to -78°C, and a solution of the starting material (3.8 g, 17 mmol, 1 eq.) in Et_2O (26 ml) at -78°C was added via a double-ended needle. The reaction mixture was stirred overnight during which the temperature was allowed to rise from-78°C to -30°C. TLC-analysis after 13h (CH_2Cl_2/acetone 9/1) showed complete conversion of the starting material. The reaction was quenched by adding a solution of NaOOH in water. This solution was prepared beforehand by adding H_2O_2 (10.5 ml, 119 mmol, 7.2 eq.) to a solution of NaOH (3.2 g, 80 mmol, 4.8 eq.) in H_2O (26 ml) at 0°C in a separate flask. The NaOOH-solution was transferred to the reaction mixture at 0°C, after which it was stirred at RT for 4h. The reaction mixture was then poured in a saturated aqueous NH_4Cl solution (100 ml), the phases were separated and the aqueous phase was extracted with EtOAc (3 x 200 ml). The combined organic phases were dried over $MgSO_4$ and concentrated. Purification was accomplished by consecutive flash column chromatography (CH_2Cl_2/acetone 95/5; Hexane/acetone 8/2; CH_2Cl_2/acetone 88/12), yielding the target material (3.6 g, 79%) as a clear, colorless oil.

Name: (5*Z*,4*S*,7*R*)-7-(((2'-methoxyethoxy)methoxy)methyl)-5-methylnona-1,5-diene-4-ol

Formula: $C_{15}H_{28}O_4$

Molecular weight: 272.4 g/mol

R_f: 0.15 (CH_2Cl_2/ acetone 9/1)

$[\alpha]_D$: -6.6 (c = 0.84 in $CHCl_3$)

ESI-MS (m/z): 255.2 (M - H_2O + H^+); 295.2 (M + Na^+)

HR-MS: calculated for ($M+NH_4^+$) 290.2326, found 290.2323 (Δ 1.0 ppm)

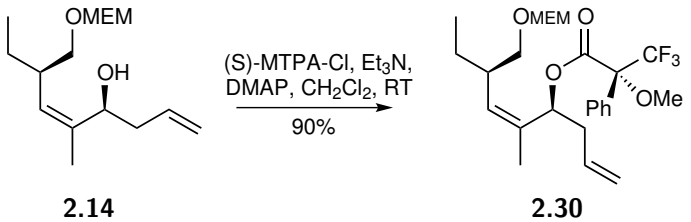
^{1}H-NMR (300 MHz; C_6D_6): δ (ppm) = 5.91 (app. dt, J = 17.2, 10.3, 6.9 Hz, 1H), 5.10 (app. ddt, J = 17.2, 3.6, 1.8 Hz, 1H), 5.03 (app. ddt, J = 10.2, 2.3, 1.1 Hz, 1H), 4.94 (app. dd, J = 9.9, 1.8 Hz, 1H), 4.64 (app. t, J = 7.2 Hz, 1H), 4.48 (app. s, 2H), 3.59-3.46 (m, 2H), 3.36 (dd, J = 9.1, 4.9 Hz, 1H), 3.33-3.26 (m, 2H), 3.14 (dd, J = 17.9, 9.0 Hz, 1H), 3.11 (s, 3H), 2.65-2.50 (m, 1H), 2.39-2.28 (m, 1H), 1.89 (d, J = 1.5 Hz, 3H), 1.36-1.21 (m, 1H), 1.14-0.97 (m, 1H), 0.78 (app. t, J = 7.3 Hz, 3H)

APT (75 MHz; C_6D_6): δ (ppm) = 140.46 (C), 136.31 (CH), 131,13 (CH), 116.87 (CH_2), 95.86 (CH_2), 72.55 (CH_2), 71.76 (CH_2), 69.25 (CH), 67.62 (CH_2), 58.97 (CH_3), 39.84 (CH), 39.37 (CH_2), 25.60 (CH_2), 18.60 (CH_3), 12.29 (CH_3)

IR (HATR): 3435 (b), 2929, 2876, 2186 (w), 2009 (w), 1982 (w), 1451, 1408, 1376, 1292, 1242, 1199, 1174, 1111 (m), 1095, 1044 (s), 1019 (s), 989 (m), 938, 911, 852 cm^{-1}

EI-MS (m/z; (%)): 155 (8), 149 (9), 127 (3), 126 (9), 125 (96), 121 (4), 111 (3), 109 (9), 108 (7), 107 (25), 105 (5), 97 (14), 96 (3), 95 (11), 94 (3), 93 (11), 91 (5), 90 (3), 89 (51), 86 (4), 84 (8), 83 (15), 81 (14), 80 (3), 79 (13), 77 (5), 71 (8), 69 (19), 67 (9), 65 (3), 60 (3), 59 (100), 57 (13), 56 (4), 55 (31), 53 (7), 51 (5), 49 (11), 46 (4), 45 (29), 44 (6), 43 (51), 42 (5), 41 (45)

5.2.8 Synthesis of (*R*)-MTPA ester 2.30



2.14 **2.30**

To a solution of **2.14** (50 mg, 0.18 mmol, 1 eq.) and 4-(*N,N*-dimethylamino)pyridine (DMAP) (2 mg, 0.02 mmol, 0.1 eq.) in pyridine (370 μl) was added (*S*)-(-)-α-methoxy-α-trifluoromethylphenylacetylchloride ((*S*)-MTPA-Cl) (52 μl; 0.28 mmol, 1.5 eq.) at RT. After 22h of stirring at RT, TLC-analysis (CH_2Cl_2/acetone 9/1)indicated complete consumption of the starting material, and the reaction mixture was poured in H_2O (10 ml) and extracted with CH_2Cl_2 (4 x 10 ml). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (pentane/ EtOAc 8/2) delivered **2.30** (81 mg, 90%) as a clear oil.

Name: (4*S*,5*Z*,7*R*)-7-(((2'-methoxyethoxy)methoxy)methyl)-5-methylnona-1,5-dien-4-yl (*R*)-3",3",3"-trifluoro-2"-methoxy-2"-phenylpropanoate

Formula: $C_{25}H_{35}F_3O_6$

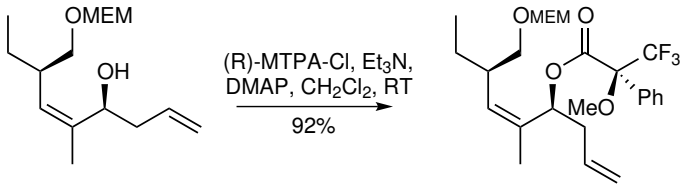
Molecular weight: 488.5 g/mol

R_f: 0.76 (CH_2Cl_2/acetone 9/1)

^{1}H-NMR (300 MHz; C_6D_6): δ (ppm) = 7.74 (2H, d, J = 7.7 Hz), 7.14-7.04 (3H, m), 6.05 (1H, dd, J = 8.4, 5.9 Hz), 5.65-5.51 (1H, m), 5.12 (1H, dd, J = 10.3, 1.0 Hz), 5.01-4.93 (2H, m), 4.67 (2H, dd , J = 7.3, 6.7 Hz), 3.75-3.64 (2H, m), 6.63-3.48 (5H, m), 3.42 (2H, app. t, J = 5.2 Hz), 3.15 (3H, s), 2.89-2.77 (1H, m), 2.49-2.39 (1H, m), 2.22-2.14 (1H, m), 1.72-1.58 (1H, m), 1.46 (3H, d, J = 1.3 Hz), 1.27-1.13 (1H, m), 0.80 (3H, app. t, J = 7.5 Hz)

APT (75 MHz; C_6D_6): δ (ppm) = 166.05 (C), 133.91 (CH), 133.67 (CH), 133.13 (C), 129.99 (3 x CH), 128.98 (C); 128.22 (2 x CH), 126.60 (C), 122.78 (C), 118.55 (CH_2), 96.23 (CH_2), 74.90 (CH), 72.61 (CH_2), 71.52 (CH_2), 67.61 (CH_2), 59.00 (CH_3), 55.97 (CH_3), 40.43 (CH), 37.65 (CH_2), 25.71 (CH_2), 18.14 (CH_3), 12.40 (CH_3)

5.2.9 Synthesis of (*S*)-MTPA ester 2.31



2.14 **2.31**

To a solution of **2.14** (50 mg, 0.18 mmol, 1 eq.) and 4-(*N,N*-dimethylamino)pyridine (DMAP) (2 mg, 0.02 mmol, 0.1 eq) in pyridine (370 μl) was added (*R*)-(-)-α-methoxy-α-trifluoromethylphenylacetylchloride ((*R*)-MTPA-Cl) (52 μl; 0.28 mmol, 1.5 eq.) at RT. After 22h of stirring at RT, TLC-analysis (CH_2Cl_2/acetone 9/1)indicated complete consumption of the starting material, and the reaction mixture was poured in H_2O (10 ml) and extracted with CH_2Cl_2 (4 x 10 ml). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (pentane/EtOAc 8/2 delivered **2.31** (83 mg, 92%) as a clear oil.

Name: (4*S*,5*Z*,7*R*)-7-(((2'-methoxyethoxy)methoxy)methyl)-5-methylnona-1,5-dien-4-yl (*S*)-3",3",3"-trifluoro-2"-methoxy-2"-phenylpropanoate

Formula: $C_{25}H_{35}F_3O_6$

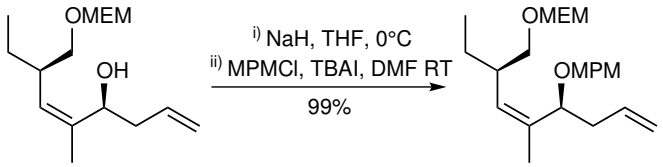
Molecular weight: 488.5 g/mol

R_f: 0.76 (CH_2Cl_2/acetone 9/1)

^{1}H-NMR (300 MHz; C_6D_6): δ (ppm) = 7.71 (2H, d, J = 7.6 Hz), 7.13-7.03 (3H, m), 6.16 (1H, app. t, J = 6.6 Hz), 5.63-5.49 (1H, m), 5.14 (1H, d, J = 10.3 Hz), 4.97-4.89 (2H, m), 4.61 (2H, dd, J = 7.7, 6.7 Hz), 3.65-3.62 (2H, m), 3.48-3.43 (5H, m), 3.41-3.37 (2H, m), 3.13 (3H, s), 2.86-2.74 (1H, m), 2.49-2.39 (1H, m), 2.21-2.12 (1H, m), 1.64 (3H, d, J = 1.3 Hz), 1.60-1.49 (1H, m), 1.24-1.09 (1H, m), 0.78 (3H, app. t, J = 7.5 Hz)

APT (75 MHz; C_6D_6): δ (ppm) = 166,22 (C); 134.14 (CH), 133.72 (C), 133.51 (CH), 133.27 (C), 130.02 (3 x CH), 128.89 (2 x CH), 126.64 (C), 122.83 (C), 118.59 (CH_2), 96.12 (CH_2), 74.56 (CH), 72.58 (CH_2), 71.55 (CH_2), 67.56 (CH_2), 58.99 (CH_3), 55.67 (CH_3), 40.41 (CH), 37.63 (CH_2), 25.65 (CH_2), 18.45 (CH_3), 12.37 (CH_3)

5.2.10 Synthesis of methoxyphenyl methyl ether 2.15



To a flask containing NaH (1.05 g, 26 mmol, 2 eq., 60m% dispersion in mineral oil) was added a solution of **2.14** (3.58 g, 13 mmol, 1 eq.) in THF (40 ml) at 0°C. The reaction mixture was stirred for 30' at RT, after which methoxyphenylmethylchloride (3,6 ml, 26 mmol, 2 eq.) was added dropwise *via* syringe, followed by a suspension of tetrabutylammoniumiodide (9.7 g, 26 mmol, 2 eq) in DMF (13 ml). The reaction was stirred at RT for 5h, after which TLC-analysis (CH_2Cl_2/acetone 9/1) showed complete conversion of the starting material. The reaction mixture was then gently poured in a separation funnel containing water (200 ml), and extracted with Et_2O (4 x 200 ml). The combined organic fractions were dried over $MgSO_4$, and concentrated. The product was purified by flash column chromatography (pentane/Et_2O 8/2), yielding the desired product **2.15** as a clear yellow oil (5.10 g, 13 mmol, 99%).

Name: (5*Z*,4*S*,7*R*)-4-((4"-methoxybenzyl)oxy)-7-(((2'-methoxyethoxy)methoxy)-methyl)-5-methylnona-1,5-diene

Formula: $C_{23}H_{36}O_5$

Molecular weight: 392.5 g/mol

R_f: 0.31 (pentane/Et_2O 6/4)

$[\alpha]_D$: -66.9 (c = 7.6 mg/ml in $CHCl_3$)

ESI-MS (m/z): 410.2 ($M + NH_4^+$)

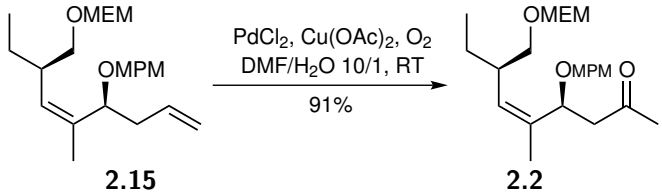
HR-MS: calculated for (M+?) ?, found ? (Δ ? ppm)

^{1}H-NMR (300 MHz; C_6D_6): δ (ppm) = 7.39 (app. d, J = 8.6 Hz, 2H), 6.86 (app. d, J = 8.9 Hz, 2H), 5.96 (dddd, J = 17.1, 10.2, 7.4, 6.8 Hz, 1H), 5.20 (dd, J = 10.3, 2.0 Hz, 1H), 5.10 (app. ddd, J = 17.1, 3.6, 1.4 Hz, 1H), 5.04 (app. ddt, J = 10.1, 2.2, 1.1 Hz, 1H), 4.61 (app. s, 2H), 4.60 (d, J = 11.7 Hz, 1H), 3.39 (dd, J = 8.1, 5.8 Hz, 1H), 4.36 (d, J = 11.7 Hz, 1H), 3.64-3.60 (m, 2H), 3.42 (app. dd, J = 6.4, 3.1 Hz, 2H), 3.39-3.34 (m, 2H), 3.32 (s, 3H), 3.12 (s, 3H), 2.71-2.52 (m, 2H), 3.42 (app. dddt, J = 14.1, 7.3, 5.9, 1.3 Hz, 1H), 1.80 (d, J = 1.3 Hz, 3H), 1.61-1.46 (m, 1H), 1.27-1.11 (m, 1H), 0.83 (app. t, J = 7.4 Hz, 3H)

APT (75 MHz; C_6D_6): δ (ppm) = 160.98 (C), 136.84 (C), 136.34 (CH), 132.35 (CH + C), 129.67 (2 x CH), 116.81 (CH_2), 114.42 (2 x CH), 96.12 (CH_2), 77.12 (CH), 72.61 (CH_2), 72.07 (CH_2), 70.18 (CH_2), 67.59 (CH_2), 59.03 (CH_3), 55.12 (CH_3), 39.79 (CH), 39.54 (CH_2), 25.92 (CH_2), 18.47 (CH_3), 12.33 (CH_3)

IR (HATR): 3008 (w), 2933 (w), 2876 (w), 1613 (w), 1513, 1462 (w), 1455 (w), 1300 (w), 1247, 1214, 1172, 1110, 1095, 1075, 1049 (m), 991 (w), 916 (w), 847 (w), 823 (w), 751 (s), 666 cm^{-1}

5.2.11 Synthesis of methylketone 2.2



2.15 **2.2**

To a solution of the diene **2.15** (5.10 g, 13 mmol, 1 eq.) in a mixture of DMF (240 ml) and water (24 ml) was added $Cu(OAc)_2$ (3.94 g, 20 mmol, 1.5 eq.) in one portion and $PdCl_2$ (582 mg, 3.3 mmol, 0.25 eq.) in different portions. The reaction mixture was bubbled using O_2 and stirred at room temperature until TLC-analysis showed complete conversion of the starting material. The reaction mixture was then poured in water (500 ml) and extracted with Et_2O (3 x 800 ml). The combined organic phases were dried over $MgSO_4$ and concentrated. After concentration, the crude product was filtered over a patch of celite, rinsed with Et_2O (200 ml), and transferred to a separation funnel containing water (300 ml) using Et_2O (100ml). The phases were separated and the aqueous phase was extracted with Et_2O (2 x 300 ml). Again, the combined organic phases were dried over $MgSO_4$ and concentrated. Purification via flash column chromatography (pentane/ Et2O 6/4) delivered methyl ketone **2.2** as a clear yellow oil (4.88 g, 12 mmol, 91%).

Name: (5*Z*,4*S*,7*R*)-4-((4"-methoxybenzyl)oxy)-7-(((2'-methoxyethoxy)methoxy)-methyl)-5-methylnon-5-en-2-one

Formula: $C_{23}H_{36}O_6$

Molecular weight: 408.5 g/mol

R_f: 0.16 (pentane/Et_2O 6/4)

$[\alpha]_D$: -43.8 ° (c = 8.0 mg/ml in $CHCl_3$)

ESI-MS (m/z): 426.2 ($M+NH_4^+$); 431.2 ($M+Na^+$)

HR-MS: calculated for ($M+NH_4^+$) 426.2850, found 426.2850 (Δ 0 ppm)

^{1}H-NMR (300 MHz; C_6D_6): δ (ppm) = 7.33 (app. d, J = 8.3 Hz, 2H), 6.82 (app. d, J = 8.4 Hz, 2H), 5.18 (app. d, J = 10.2 Hz, 1H), 5.01 (dd, J = 9.4, 2.9 Hz, 1H), 4.60 (app. s, 2H), 4.55 (d, J = 11.4 Hz, 1H), 4.38 (d, J = 11.4 Hz, 1H), 3.66-3.58 (m, 2H), 3.48-3.34 (m, 4H), 3.30 (s, 3H), 3.13 (s, 3H), 2.78 (dd, J = 15.4, 9.4 Hz, 1H), 2.78-2.65 (m, 1H), 2.12 (dd, J = 15.4, 3.0 Hz,

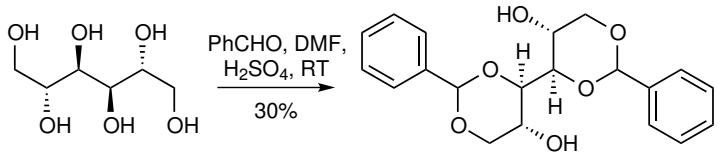
1H), 1.80 (s, 3H), 1.75 (d, J = 1.0 Hz, 3H), 1.59-1.43 (m, 1H), 1.24-1.07 (m, 1H), 0.81 (app. t, J = 7.4 Hz, 3H)

APT (75 MHz; C_6D_6): δ (ppm) = 205.02 (C), 160.04 (C), 136.12 (C), 132.60 (CH), 131.90 (C), 129.89 (2 x CH), 114.42 (2 x CH), 96.11 (CH_2), 73.90 (CH), 72.62 (CH_2), 72.02 (CH_2), 70.60 (CH_2), 67.60 (CH_2), 59.03 (CH_3), 55.11 (CH_3), 48.30 (CH_2), 39.98 (CH), 31.17 (CH_3), 25.76 (CH_2), 18.54 (CH_3), 12.27 (CH_3)

IR (HATR): 3013 (w), 2957 (w), 2933 (w), 2871 (w), 1714, 1611 (w), 1514, 1462 (w), 1454 (w), 1358 (w), 1300 (w), 1248, 1216, 1173, 1092, 1049, 850 (w), 822 (w), 752 (s), 666 (w) cm^{-1}

5.3 Synthesis of the C_1-C_3 aldehyde

5.3.1 Synthesis of 1,3-4,6 dibenzylidene mannitol 2.35



2.34 **2.35**

To a solution of D-mannitol (**2.34**) (50 g, 275 mmol, 1 eq.) in DMF (150 ml) was added benzaldehyde (60 ml, 591 mmol, 2.15 eq.). Then, concentrated H_2SO_4 (10 ml, 183 mmol, 0.66 eq.) was added dropwise and the resulting suspension was stirred for 3 days at room temperature. After 3 days, the reaction mixture was poured in a mixture of K_2CO_3 (15 g) in ice water (1.5 L). Next, petroleum ether (250 ml) was added and the resulting mixture was stirred until all the ice was melted. A white precipitate was formed, which was filtered off and washed with petroleum ether (3 x 100 ml). The resulting white solid was first triturated from $CHCl_3$, then recrystallised from MeOH to deliver **2.35** as white needles (29.5 g, 82.3 mmol, 30%).

Name: (4*R*,5*R*)-4-[(4'*R*,5'*R*)-5'-hydroxy-2'-phenyl-1',3'-dioxan-4'-yl]-2-phenyl-1,3-dioxan-5-ol

Formula: $C_{20}H_{22}O_6$

Molecular weight: 358.4 g/mol

R_f: 0.32 (hexane/EtOAc 3/7)

Melting point: 198°C

$[\alpha]_D$: -8.2 (c = 1.0 mg/ml in acetone)

ESI-MS (m/z): 359.2 ($M+H^+$)

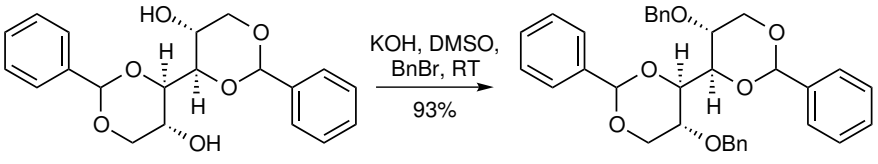
HR-MS: calculated for ($M+H^+$) 359.1489, found 359.1492 (Δ 0.8 ppm)

^{1}H-NMR (500 MHz; aceton–d_6): δ (ppm) = 7.52-7.48 (m, 4H), 7.37-7.30 (m, 6H), 5.55 (s, 2H), 4.59 (bd, J = 5.3 Hz, 2H), 4.28-4.24 (m, 2H), 4.12-4.05 (m, 4H), 3.69-3.61 (m, 2H)

APT (125 MHz; aceton–d_6): δ (ppm) = 139.65 (2 x C), 129.22 (4 x CH), 128.66 (4 x CH), 127.10 (4 x CH), 101.64 (2 x CH), 79.71 (2 x CH), 72.17 (2 x CH_2), 60.36 (2 x CH)

IR (HATR): 3473, 2977, 2863, 2506 (w) 2155, 2021, 1990, 1977, 1447, 1411, 1396, 1377, 1364, 1223, 1101, 1070, 1047 (s), 1026 (s), 1003, 968, 925, 778, 747, 736, 698, 630 cm^{-1}

5.3.2 Synthesis of 2.36



2.35 **2.36**

To a suspension of KOH (8.98 g, 160 mmol, 8 eq.) in DMSO (40 ml) were added **2.35** (7.16 g, 20 mmol, 1 eq.) and benzylbromide (7.14 ml, 60 mmol, 3 eq.) at room temperature. The reaction mixture was stirred for 4h at RT, after which TLC-analysis (CH_2Cl_2/MeOH 96/4; micro-extraction from Et_2O:water) indicated full conversion of the starting material. The reaction mixture was poured in water (400 ml) and extracted with CH_2Cl_2 (4 x 400 ml). The combined organic layers were washed with a saturated aqueous solution of NaCl (400 ml), then dried over $MgSO_4$, and concentrated. Flash column chromatography (pentane/Et_2O 8/2) and recrystallisation from $CHCl_3$:hexane 6:1 delivered **2.36** as white crystals (10.0 g, 18.6 mmol, 93%).

Name: (4*R*,5*R*)-4-[(4'*R*,5'*R*)-5'-hydroxymethylphenyl-2'-phenyl-1',3'-dioxan-4'-yl]-2-phenyl-5-hydroxymethylphenyl-1,3-dioxan

Formula: $C_{34}H_{34}O_6$

Molecular weight: 538.6 g/mol

R_f: 0.18 (pentane/Et_2O 8/2)

Melting point: 110°C

ESI-MS (m/z): 539.2 ($M+H^+$)

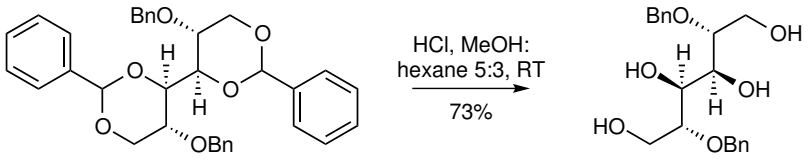
HR-MS: calculated for ($M+H^+$) 539.2428, found 539.2432 (Δ 0.7 ppm)

^{1}H-NMR (500 MHz; aceton–d_6): δ (ppm) = 7.46-7.23 (m, 20H), 5.56 (s, 2H), 4.70 (d, J = 11.9, 2H, A part of AB-spinsystem), 4.67 (d, J = 12.0, 2H, B part of AB-spinsystem), 4.42 (dd, J = 10.6, 5.2 Hz, 2H), 4.14 (dd, J = 10.5, 1.4 Hz, 2H), 3.95 (app. tdd, 10.3, 5.2, 1.3 Hz, 2H), 3.69 (app. t, J = 10.4 Hz, 2H)

APT (125 MHz; aceton–d_6): δ (ppm) = 139.48 (2 x C), 139.28 (2 x C), 129.35 (2 x CH), 129.17 (4 x CH), 128.97 (2 x CH), 128.80 (2 x CH), 128.72 (2 x CH), 128.57 (2 x CH), 128.41 (2 x CH), 127.13 (4 x CH), 101.63 (2 x CH), 78.23 (2 x CH), 72.84 (2 x CH_2), 70.03 (2 x CH_2), 67.55 (2 x CH)

IR (HATR): 2868, 2852, 2171, 2026, 1977, 1456, 1372, 1220, 1091 (s), 1024 (s), 1012 (s), 964, 743 (s), 696 (s) cm^{-1}

5.3.3 Synthesis of tetrol 2.37



2.36 **2.37**

Compound **2.36** (6 g, 11.1 mmol, 1 eq.) was dissolved in a mixture of MeOH (560 ml) and hexane (337 ml). Concentrated HCl (2.7 ml, 12 M, 2.9 eq.) was added, upon which a clear reaction mixture was formed. After stirring for 15h, water (45 ml) was added, the biphasic mixture was transferred to a separation funnel, and the layers were separated. The aqueous layer was basified with a saturated aqueous solution of Na_2CO_3 (21 ml) and further with solid Na_2CO_3 until the pH reached 8-9. The salts were filtered, the filtrate was concentrated and taken up again in boiling EtOAc. The solids were filtered out, and the filtrate was concentrated again. The residu was subjected to column chromatography (4% MeOH in EtOAc), which, after drying overnight *in vacuo*, delivered tetrol **2.37** (2.93 g, 8.1 mmol, 73%) as white, fluffy solids.

Name: (2*R*,3*S*,4*S*,5*R*)-2,5-bis(benzyloxy)hexane-1,3,4,6-tetraol

Formula: $C_{20}H_{26}O_6$

Molecular weight: 362.4 g/mol

R_f: 0.23 (4% MeOH in EtOAc)

Melting point: 121°C

ESI-MS (m/z): 363.2 ($M+H^+$)

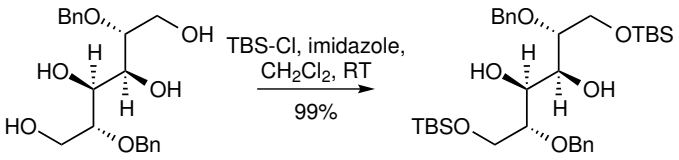
HR-MS: calculated for ($M+H^+$) 363.1802, found 363.1805 (Δ 0.8 ppm)

^{1}H-NMR (500 MHz; DMSO): δ (ppm) = 7.36-7.29 (m, 8H), 7.27-7.22 (m, 2H), 4.70 (d, J = 11.6 Hz, 2H), 4.53 (d, J = 11.6 Hz, 2H), 4.47 (dd, J = 5.9, 5.1 Hz, 2H), 4.43 (d, J = 7.7 Hz, 2H), 3.82 (ddd, J = 11.7, 4.9, 3.2 Hz, 2H), 3.75 (app. t, J = 8.1 Hz, 2H), 3.57 (app. dt, J = 11.4, 5.7 Hz, 2H), 3.47 (ddd, J = 8.2 Hz, 5.0, 3.1 Hz, 2H)

APT (125 MHz; DMSO): δ (ppm) = 139.31 (2 x C), 128.03 (4 x CH), 127.38 (4 x CH), 127.10 (2 x CH), 80.04 (2 x CH), 71.50 (2 x CH_2), 68.46 (2 x CH), 61.04 (2 x CH_2)

IR (HATR): 3468, 3370, 3258, 2946, 2920, 2873, 1463, 1452, 1408, 1370, 1095 (s), 1075 (s), 1034 (s), 1024 (s), 995, 850 (s), 750, 738 (s), 698 cm^{-1}

5.3.4 Synthesis of diol 2.38



2.37 **2.38**

To a solution of compound **2.37** (1g, 2.76 mmol, 1 eq.) in CH_2Cl_2 (28 ml) was added imidazole (470 mg, 6.90 mmol, 2.5 eq.) and the mixture was stirred for 5' at room temperature. Then, the solution was cooled down to 0C and a solution of TBS-Cl in CH_2Cl_2 (6.35 ml, 1M solution, 6.35 mmol, 2.3 eq.) was added *via* a cannula. The reaction mixture was stirred for 3h at room temperature, poured in water (100 ml) and diluted with CH_2Cl_2 (50 ml). The layers were separated and the aqueous one was extracted with CH_2Cl_2 (2 x 50 ml). The combined organic layers were dried over $MgSO_4$ and concentrated. The residu was subjected to flash column chromatography (hexane/EtOAc 8/2) to deliver **2.38** (1.62 g, 2.74 mmol, 99%) as a colorless oil.

Name: (2*R*,3*S*,4*S*,5*R*)-2,5-bis(benzyloxy)hexane-1,6-bis(*tert*-butyl-dimethylsilyloxy)-3,4-diol

Formula: $C_{32}H_{54}O_6Si_2$

Molecular weight: 590.9 g/mol

R_f: 0.57 (Hexane/EtOAc 8/2)

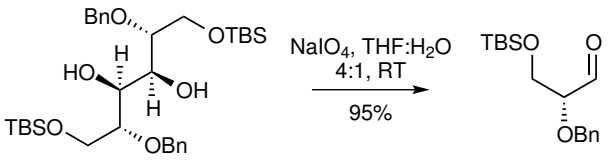
ESI-MS (m/z): 591.3 ($M+H^+$)

HR-MS: calculated for ($M+H^+$) 591.3532, found 591.3527 (Δ 0.8 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.36-7.26 (m, 10H), 4.74 (d, J = 11.5 Hz, 2H), 4.63 (d, J = 11.5 Hz, 2H), 3.93 (app. t, J = 5.5 Hz, 2H), 3.87 (dd, J = 10.8, 5.0 Hz, 2H), 3.78 (dd, J = 10.8, 5.3 Hz, 2H), 3.62 (app. dt, J = 6.7, 5.1 Hz, 2H), 3.22 (bd, J = 5.4 Hz, 2H), 0.89 (s, 18H), 0.06 (s, 12H)

APT (125 MHz; DMSO): δ (ppm) = 138.56 (2 x C), 128.52 (4 x CH), 128.08 (4 x CH), 127.83 (2 x CH), 80.52 (2 x CH), 73.43 (2 x CH_2), 70.22 (2 x CH), 63.80 (2 x CH_2) 26.03 (6 x CH_3), 18.38 (2 x C), -5.31 (2 x CH_3), -5.35 (2 x CH_3)

5.3.5 Synthesis of aldehyde 2.4



2.38 **2.4**

To a solution of diol **2.38** (500 mg, 0.85 mmol, 1 eq.) in a mixture of THF (14 ml) and water (3.4 ml) was added $NaIO_4$ and the reaction mixture was stirred at room temperature for 3h, after which TLC-analysis (hexane/EtOAc 9/1) indicated full conversion of the starting material. The reaction mixture was diluted with Et_2O (35 ml) and washed with water (3 x 10 ml) and brine (10 ml). After drying over $MgSO_4$ and concentration, the crude aldehyde **2.4** was obtained (473 mg, 1.6 mmol, 95%) as a colorless oil, which was used as such in the next reaction

Name: (*R*)-2-benzyloxy-3-(tert-butyldimethylsilyloxy)propanal

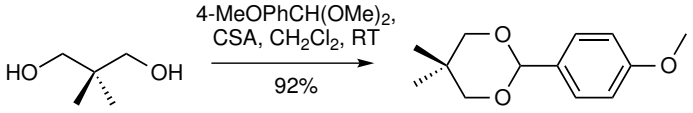
Formula: $C_{16}H_{26}O_3Si$

Molecular weight: 294.5 g/mol

R_f: 0.37 (Hexane/EtOAc 9/1)

5.4 Synthesis of the MPM protected C_5-C_{11} fragment

5.4.1 Synthesis of acetal 2.41



2.39 **2.41**

To a solution of **2.39** (5g, 48.0 mmol, 1 eq.) in CH_2Cl_2 (130 ml) were added anisaldehyde-dimethyl acetal (9 ml, 52.8 mmol, 1.1 eq.) and camphorsulfonic acid (134 mg, 0.58 mmol, 0.012 eq.) and the resulting solution was stirred at room temperature until TLC-analysis (pentane/ EtOAc 1/1) showed full conversion of the starting material (2h). The mixture was transferred to a separation funnel, diluted with CH_2Cl_2 (250 ml) and washed with an aqueous solution, saturated in $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated. Flash column chromatography (hexane/EtOAc 9/1) delivered **2.41** (9.8 g, 44.2 mmol, 92%) as white solid.

Name: 2-(4'-methoxyphenyl)-5,5-dimethyl-1,3-dioxane

Formula: $C_{13}H_{18}O_3$

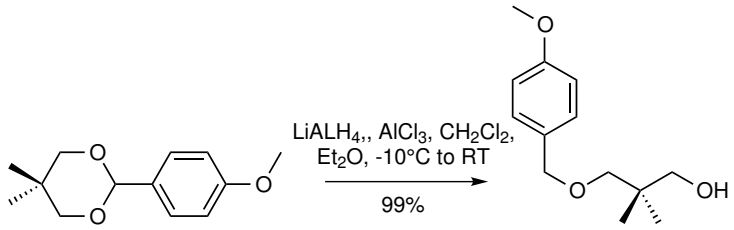
Molecular weight: 222.3 g/mol

R_f: 0.24 (hexane/EtOAc 9/1)

ESI-MS (m/z): 223.1 ($M+H^+$)

^{1}H-NMR (300 MHz; DMSO$-d_6$): δ (ppm) = 7.37-7.31 (m, 2H), 6.94-6.87 (m, 2H), 5.34 (s, 1H), 3.75 (s, 3H), 3.65 (d, J = 10.6 Hz, 2H, A part of AB-spinsystem), 3.59 (d, J = 10.6 Hz, 2H, B part of AB spinsystem), 1.18 (s, 3H), 0.74 (s, 3H)

5.4.2 Synthesis of alcohol 2.42



2.41 **2.42**

To a solution of acetal **2.41** (9.8 g, 44.1 mmol, 1 eq.) in a mixture of CH_2Cl_2 (88 ml) and Et_2O (88 ml) at -10°C was added $LiAlH_4$ (1.68 g, 44.1 mmol, 1 eq.) in one portion. Then, a cooled (0°C) solution of $AlCl_3$ (5.9 g, 44.1 mmol, 1 eq.) in Et_2O (33 ml) was added and the RM was stirred for 10' at -10°C, and 1h at room temperature. Upon completion of the reaction (TLC analysis pentane/ Et_2O) the mixture was cooled to 0°C, and quenched by the addition of first EtOAc (43 ml), and then water (130 ml). The mixture was transferred to a separation funnel, the layers were separated and the aq. one was extracted with CH_2Cl_2 (2 x 200 ml). The combined organic phases were washed with brine, dried over $MgSO_4$ and concentrated. Flash column chromatography (pentane/EtOAc 8/2) delivered alcohol **2.42** (9.76g, 43.9 mmol, 99%)

Name: 3-((4'-methoxybenzyl)oxy)-2,2-dimethylpropan-1-ol

Formula: $C_{13}H_{20}O_3$

Molecular weight: 224.3 g/mol

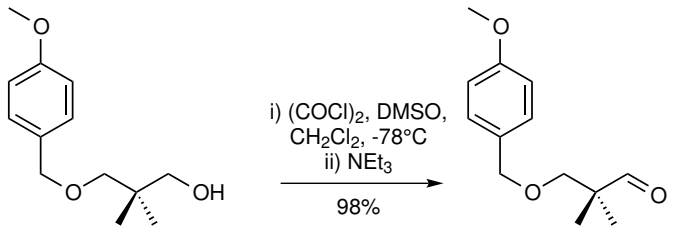
R_f: 0.19 (pentane/EtOAc 8/2)

ESI-MS (m/z): 247.1 ($M+Na^+$)

^{1}H-NMR (300 MHz; DMSO$-d_6$): δ (ppm) = 7.26-7.20 (m, 2H), 6.93-6.86 (m, 2H), 4.42 (t, J = 5.4 Hz, 1H), 4.37 (s, 2H), 3.74 (s, 3H), 3.16 (d, J = 5.4 Hz, 2H), 3.13 (s, 3H), 0.80 (s, 6H)

APT (75 MHz; DMSO$-d_6$): δ (ppm) = 158.56 (C), 130.80 (C), 128.79 (2 x CH), 113.59 (2 x CH), 75.75 (CH_2), 72.06 (CH_2), 67.31 (CH_2), 55.02 (CH_3), 36.61 (C), 21.82 (2 x CH_3)

5.4.3 Synthesis of aldehyde 2.43



2.42 **2.43**

To a solution of oxalylchloride (4.3 ml, 50.6 mmol, 2.2 eq.) in CH_2Cl_2 (125 ml) at -78°C was added dimethylsulfoxide (7.8 ml, 110 mmol, 4.8 eq.) dropwise. Then, alcohol **2.42** (5.15 g, 23 mmol, 1 eq.) was added dropwise as a solution in CH_2Cl_2 (46 ml) and the resulting mixture was stirred for 15' at -78°C. Next, Et_3N (16 ml, 115 mmol, 5 eq.) was added dropwise, the solution was stirred at the same temperature for 10', then allowed to warm to RT and stirred for 5h. The reaction was quenched by addition of HCl (240 ml, 0.1M). The layers were separated, and the aqueous one was extracted with CH_2Cl_2 (2 x 250 ml). The combined organic phases were dried over MgSO4, concentrated and subjected to flash column chromatography (pentane/ Et_2O 75/25), delivering aldehyde **2.43** (5 g, 22.9 mmol, 98%)

Name: 3-((4'-methoxybenzyl)oxy)-2,2-dimethylpropanal

Formula: $C_{13}H_{18}O_3$

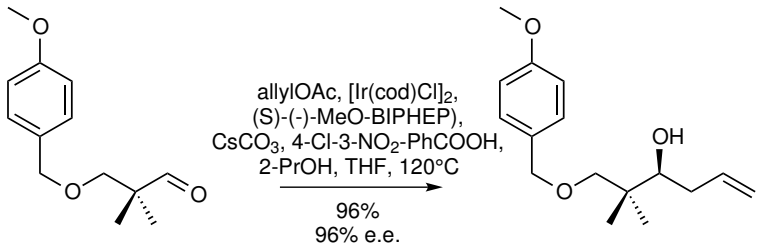
Molecular weight: 222.3 g/mol

R_f: 0.44 (pentane/Et_2O 7/3)

^{1}H-NMR (300 MHz; DMSO$-d_6$): δ (ppm) = 9.47 (s, 1H), 7.24-7.17 (m, 2H), 6.93-6.87 (m, 2H), 4.38 (s, 2H), 3.74 (s, 3H), 3.43 (s, 2H), 0.98 (s, 6H)

APT (75 MHz; DMSO$-d_6$): δ (ppm) = 205.45 (CH), 158.72 (C), 130.00 (C), 129.05 (2 xCH), 113.66 (2 x CH), 74.13 (CH2), 72.09 (CH2), 55.02 (CH3), 46.78 (C), 18.51 (2 x CH3)

5.4.4 Synthesis of homoallylic alcohol 2.44



2.43 **2.44**

In a pressure tube, a mixture of $[Ir(cod)Cl]_2$ (93 mg, 0.14 mmol, 0.025 eq.), (*S*)-(-)-(6,6'-dimethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine) (180 mg, 0.28 mmol, 0.05 eq.), Cs_2CO_3 (360 mg, 1.11 mmol, 0.2 eq.), 3-chloro-4-nitrobenzoic acid (111 mg, 0.55 mmol, 0.1 eq.) and aldehyde **2.43** (1.23 g, 5.53 mmol, 1 eq.) was dissolved in THF (27 ml). Then, allyl acetate (5.95 ml, 55.3 mmol, 10 eq.) and 2-propanol (850 μl, 11.1 mmol, 2 eq.) were added, the tube was sealed, heated to 120°C and stirred at that temperature for 66h, after which TLC-analysis (hexane/ EtOAc 8/2) indicated completion of the reaction. Then, the reaction mixture was evaporated on silica. Flash column chromatography (solid loading; hexane to

hexane/ EtOAc 9/1) delivered homoallylic alcohol **2.44** (1.4 g, 5.31 mmol, 96%) as colorless oil.

The enantiomeric excess was measured on a Chiralpak IA column, using a 30' isocratic gradient of n-hexane/EtOH 98:2.

Name: (*S*)-1-((4'-methoxybenzyl)oxy)-2,2-dimethylhex-5-en-3-ol

Formula: $C_{16}H_{24}O_3$

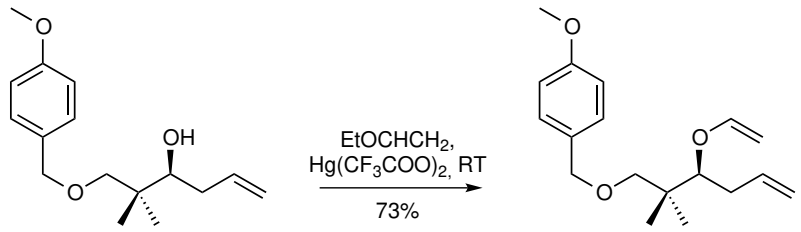
Molecular weight: 264.4 g/mol

R_f: 0.31 (hexane/EtOAc 8/2)

ESI-MS (m/z): 287.1 ($M+Na^+$)

^{1}H-NMR (300 MHz; $CDCl_3$): δ (ppm) = 7.26-7.20 (m, 2H), 6.90-6.84 (m, 2H), 5.92 (dddd, J = 17.0, 10.2, 7.2, 6.7 Hz, 1H), 5.15-5.04 (m, 2H), 4.44 (app. s, 2H), 3.81 (s, 3H), 3.51 (ddd, J = 10.3, 3.5, 2.6 Hz, 1H), 3.35 (d, J = 8.9 Hz, 1H, A part of AB-spinsystem), 3.26 (d, J = 8.9 Hz, 1H, B part of AB-spinsystem), 3.10 (d, J = 3.8 Hz, 1H), 2.32-2.21 (m, 1H), 2.11-1.99 (m, 1H), 0.92 (s, 3H), 0.91 (s, 3H)

5.4.5 Synthesis of enol ether 2.40



2.44 **2.40**

To a solution of alcohol **2.44** (730 mg, 2.77 mmol, 1 eq.) in ethyl vinylether (41 ml) was added mercury(II)trifluoroacetate (236 mg, 0.55 mmol, 0.2 eq.) and the reaction mixture was stirred for 5 days at room temperature. A saturated

aqueous solution of $NaHCO_3$ (50 ml)was added to the mixture, the phases were separated and the aqueous one was extracted with Et_2O (3 x 40 ml). The combined organic phases were dried over $MgSO_4$, concentrated and subjected to flash column chromatography (hexane/ Et_2O 95/5) to yield enol ether **2.40** (587 mg, 2.02 mmol, 73%) as a colorless oil.

Name: (3*S*)-1-(((2,2-dimethyl-3-(vinyloxy)hex-5-en-1-yl)oxy)methyl)-4-methoxybenzene

Formula: $C_{18}H_{26}O_3$

Molecular weight: 290.4 g/mol

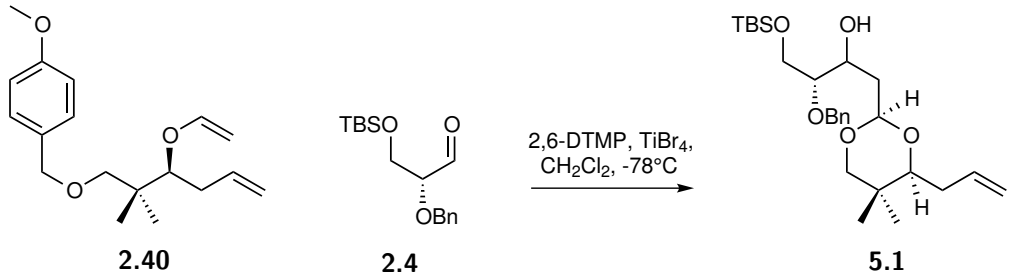
R_f: 0.52 (hexane/EtOAc 8/2)

^{1}H-NMR (300 MHz; $CDCl_3$): δ (ppm) = 7.27-7.21 (m, 2H), 6.91-6.84 (m, 2H), 6.27 (dd, J = 13.9, 6.4 Hz, 1H), 5.85 (app. ddt, J = 17.1, 10.1, 7.0 Hz, 1H), 5.11-4.99 (m, 2H), 4.42 (d, J = 11.6 Hz, 1H, A part of AB-spinsystem), 4.35 (d, J = 11.6 Hz, 1H, B part of AB-spinsystem), 4.26 (dd, J = 13.9, 1.3 Hz, 1H), 3.84-3.79 (m, 4H), 3.75 (dd, J = 6.8, 5.9 Hz, 1H), 3.28 (d, J = 8.8 Hz, 1H, A part of AB-spinsystem), 3.09 (d, J = 8.8 Hz, 1H, B part of AB-spinsystem), 2.30-2.22 (m, 2H), 0.93 (s, 3H), 0.91 (s, 3H)

APT (75 MHz; $CDCl_3$): δ (ppm) = 159.19 (C), 154.50 (CH), 136.24 (CH), 130.94 (C), 129.24 (2 x CH), 116.79 (CH_2), 113.82 (2 x CH), 86.73 (CH_2), 85.22 (CH), 76.72 (CH_2), 72.83 (CH_2), 55.40 (CH_3), 39.71 (CH), 34.89 (CH_2), 21.99 (CH_3), 20.44 (CH_3)

5.5 First attempt on the MAP reaction

5.5.1 Synthesis of acetal 5.1



2.40 **2.4** **5.1**

To a solution of enol ether **2.40** (50 mg, 0.17 mmol, 1 eq.), aldehyde **2.4** (119 mg, 0.40 mmol, 2.3 eq.) and 2,6-di-t-butyl-4-methyl-pyridine (53 mg, 0.26 mmol, 1.5 eq.) in CH_2Cl_2 (1.7 ml), was added $TiBr_4$ (1 ml, 0.34 mmol, 0.34 M, 2 eq.) at -78°C. The reaction mixture was stirred for 15 minutes, after which TLC-analysis (hexane/ EtOAc 9/1) showed full conversion of the enol ether. The reaction was quenched by the careful addition of a saturated aqueous solution of $NaHCO_3$ (5 ml), and water (5 ml) and diluted with CH_2Cl_2 (10 ml). The layers were separated, and the aqueous one was extracted with CH_2Cl_2 (3 x 10 ml). The combined organic phases were dried over MgSO4, concentrated and subjected to flash column chromatography (hexane/ EtOAc 8/2), resulting in isolation of one pure diastereomer of acetal **5.1** (stereochemistry not assigned), while the other one was contaminated with other compounds (not reported).

Formula: $C_{34}H_{53}O_6Si$

Molecular weight: 665.8 g/mol

R_f: 0.10 (hexane/ EtOAc 9/1)

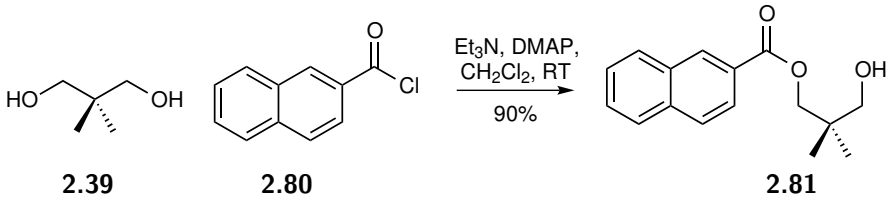
^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.37-7.27 (m, 5H), 5.85 (dddd, J = 17.2, 10.2, 7.1, 6.3 HZ, 1H), 5.06 (ddd, J = 17.2, 3.4, 1.6 Hz, 1H), 5.02 (app. ddt, J = 10.2, 2.1, 1.1 Hz, 1H), 4.75 (d, J = 11.6 Hz, 1H, A part of AB-spinsystem), 4.74 (dd, J = 6.0, 3.8 Hz, 1H), 4.60 (d, J = 11.6 Hz, 1H, B

part of AB-spinsystem), 4.03 (app. dt, J = 9.5, 3.1 Hz, 1H), 3.84 (dd, J = 10.6, 5.4 Hz, 1H), 3.77 (dd, J = 10.6, 5.8 Hz, 1H), 3.55 (d, J = 11.1 Hz, 1H), 3.43 (app. td, J = 5.6, 3.4 Hz, 1H), 3.38 (d, J = 11.1 Hz, 1H), 3.33 (dd, J = 9.9, 2.7 Hz, 1H), 2.87 (bs, 1H), 2.22-2.16 (m, 1H), 2.15-2.07 (m, 1H), 1.91 (ddd, J = 14.1, 9.6, 3.9 Hz, 1H), 1.83 (ddd, J = 14.1, 6.0, 2.9 Hz, 1H), 1.05 (s, 3H), 0.90 (s, 9H), 0.72 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 138.69 (C), 135.83 (CH), 128.47 (2 x CH), 128.17 (2 x CH), 127.80 (CH), 116.48 (CH2), 101.11 (CH), 84.64 (CH), 81.73 (CH), 78.57 (CH2), 73.25 (CH2), 67.96 (CH), 63.25 (CH2), 38.62 (CH2), 34.02 (CH2), 32.94 (C), 26.05 (3 x CH3), 21.66 (CH3), 18.72 (CH3), 18.38 (C), -5.30 (CH3), -5.33 (CH3)

5.6 Synthesis of the naphtoyl protected C_5-C_{11} fragment

5.6.1 Synthesis of ester 2.81



2.39 **2.80** **2.81**

To a solution of neopentylglycol **2.39** (8.2 g, 78.7 mmol, 3 eq.) in CH_2Cl_2 (47 ml) were added Et_3N (7.3 ml, 52.5 mmol, 2 eq.) and DMAP (160 mg, 1.3 mmol, 0.05 eq.) To this mixture, a solution of naphtoylchloride **2.80** (5 g, 26.2 mmol, 1 eq.) in CH_2Cl_2 (26 ml) was added via cannula. The flask was rinsed with CH_2Cl_2 (2 x 2 ml), and the resulting mixture was stirred for 6 days at room temperature. The reaction was quenched by addition of an aqueous saturated $NaHCO_3$-solution. The phases were separated and the aqueous one was extracted further with CH_2Cl_2 (3 x 20 ml). The combined organic phases were dried over $MgSO_4$, concentrated and subjected to flash column chromatography (hexane/EtOAc 65/35), delivering alcohol **2.81** (6.16g, 23.6 mmol, 90%) as white solids.

Name: 3-hydroxy-2,2-dimethyl-2-naphtoate

Formula: $C_{16}H_{18}O_3$

Molecular weight: 258.3 g/mol

R_f: 0.31 (hexane/EtOAc 65/35)

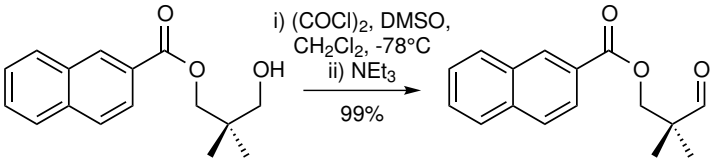
Melting point: 73°C

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 8.67 (app. s, 1H), 8.13-8.05 (m, 2H), 8.00 (app. t, J = 9.0 Hz, 2H), 7.67-7.58 (m, 2H), 4.22 (s, 2H), 3.87 (bs, 1H), 3.51 (d, J = 5.34 Hz, 2H), 1.06 (s, 6H))

APT (125 MHz; DMSO): δ (ppm) = 166.93 (C), 136.43 (C), 133.51 (C), 131.47 (CH), 130.18 (CH), 129.21 (CH), 129.14 (CH), 128.78 (C), 128.63 (CH), 127.69 (CH), 125.88 (CH), 70.75 (CH2), 68.47 (CH_2), 37.13 (C), 21.97 (2 x CH_3)

IR (HATR): 3504, 3462, 2956, 2925, 1682 (s), 1630, 1470, 1372, 1295, 1274 (s), 1230 (s), 1197 (s), cm^{-1}

5.6.2 Synthesis of aldehyde 2.82



2.81 **2.82**

To a solution of oxalylchloride (360 μl, 4.26 mmol, 2.2 eq.) in CH_2Cl_2 (11 ml) at -78°C was added dimethylsulfoxide (660 μl, 9.29 mmol, 4.8 eq.) dropwise. Then, alcohol **2.42** (500 mg, 1.94 mmol, 1 eq.) was added dropwise as a solution in CH_2Cl_2 (4 ml) and the resulting mixture was stirred for 15' at -78°C. Next, Et_3N (1.35 ml, 9.68 mmol, 5 eq.) was added dropwise, the solution was stirred at the same temperature for 10', then allowed to warm to RT and stirred for 1h. The reaction was poured into water (50 ml) and diluted with CH_2Cl_2 (40 ml). The layers were separated, and the aqueous one was extracted with CH_2Cl_2 (2 x 50 ml). The combined organic phases were dried over MgSO4, concentrated and subjected to flash column chromatography (hexane/ EtOAc 9/1), delivering aldehyde **2.82** (490 mg, 1.90 mmol, 99%)

Name: 2,2-dimethyl-3-oxopropyl 2'-naphthoate

Formula: $C_{16}H_{16}O_3$

Molecular weight: 256.3 g/mol

R_f: 0.29 (hexane/ EtOAc 9/1)

Melting point: 49°C

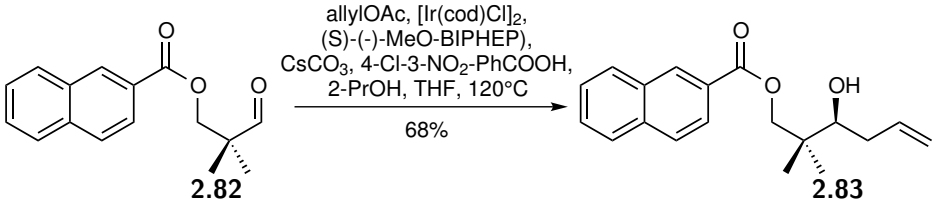
ESI-MS (m/z): 257.2 ($M+H^+$)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 9.69 (s, 1H), 8.55 (dd, J = 1.6, 0.6 Hz, 1H), 8.00 (dd, 8.6, 1.7 Hz, 1H), 7.97-7.94 (m, 1H), 7.90-7.86 (m, 2H), 7.60 (ddd, J = 8.2, 6.8, 1.4 Hz, 1H), 7.55 (ddd, J = 8.1, 6.8, 1.3 HZ, 1H), 4.44 (s, 2H), 1.25 (s, 6H)

APT (75 MHz; DMSO$-d_6$): δ (ppm) = 203.63 (CH), 166.52 (C), 135.79 (C), 132.59 (C), 131.34 (CH), 129.55 (CH), 128.56 (CH), 128.43 (CH), 127.93 (CH), 127.02 (C), 126.89 (CH), 125.23 (CH), 68.61 (CH_2), 46.79 (C), 19.17 (2 x CH_3)

IR (HATR): 2974 (w), 1726, 1708 (s), 1469, 1368, 1352, 1282 (s), 1228, 1195 (s), 1129, 1093 (s), 971, 919, 879, 837, 780 (s), 763 (s) cm^{-1}

5.6.3 Synthesis of homoallylic alcohol 2.83



In a pressure tube, a mixture of $[Ir(cod)Cl]_2$ (53 mg, 0.08 mmol, 0.025 eq.), (*S*)-(-)-(6,6'-dimethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine) (102 mg, 0.16 mmol, 0.05 eq.), Cs_2CO_3 (204 mg, 0.63 mmol, 0.2 eq.), 3-chloro-4-nitrobenzoic acid (63 mg, 0.31 mmol, 0.1 eq.) and aldehyde **2.82** (803 mg, 3.13 mmol, 1 eq.) was dissolved in THF (15 ml). Then, allyl acetate (3.37 ml, 31.3 mmol, 10 eq.) and 2-propanol (480 μl, 6.3 mmol, 2 eq.) were added, the tube was sealed, heated to 120°C and stirred at that temperature for 66h, after which TLC-analysis (hexane/ EtOAc 8/2) indicated completion of the reaction. Then, the reaction mixture was evaporated on silica. Flash column chromatography (solid loading; hexane to

hexane/ EtOAc 9/1) delivered homoallylic alcohol **2.83** (632 mg, 2.10 mmol, 68%) as white solid.

The enantiomeric excess (98%) was measured on a Chiralcel OD-H column, using a 30' isocratic gradient of n-hexane/EtOH 98:2.

Name: (3*S*)-3-hydroxy-2,2-dimethylhex-5-en-1-yl 2'-naphthoate

Formula: $C_{19}H_{22}O_3$

Molecular weight: 298.4 g/mol

R_f: 0.30 (hexane/EtOAc 8/2)

Melting point: 46°C

ESI-MS (m/z): 299.2 ($M+H^+$)

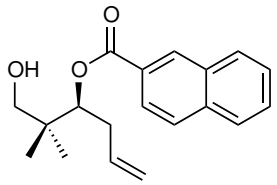
HR-MS: calculated for ($M+H^+$) 299.1642, found 299.1640 (Δ 0.6 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 8.60 (d, J = 1.7 Hz, 1H), 8.06 (dd, J = 8.6, 1.9 Hz, 1H), 7.97 (app. dd, J = 8.1, 0.8 Hz, 1H), 7.91-7.78 (m, 2H), 7.60 (ddd, J = 8.2, 6.8, 1.4 Hz, 1H), 7.55 (ddd, J = 8.1, 6.8, 1.4 Hz, 1H), 5.90 (dddd, J = 17.1, 10.2, 8.2, 5.8 Hz, 1H), 5.20-4.13 (m, 2H), 4.48 (d, J = 10.9 Hz, 1H), 4.13 (d, J = 11.0 Hz, 1H), 3.58 (dd, J = 10.6, 2.2 Hz, 1H), 2.42 (dddd, J = 14.0, 5.7, 3.8, 1.7 Hz, 1H), 2.19 (bs, 1H), 2.14 (app. dddt, J = 14.0, 10.5, 8.3, 1.0 Hz, 1H), 1.10 (s, 3H), 1.07 (s, 3H)

APT (125 MHz; aceton−d_6): δ (ppm) = 167.12 (C), 136.26 (CH), 135.71 (C), 132.63 (C), 131.23 (CH), 129.52 (CH), 128.45 (CH), 128.37 (CH), 127.92 (CH), 127.59 (C), 126.84 (CH), 125.32 (CH), 118.16 (CH_2), 74.27 (CH), 71.28 (CH_2), 38.87 (C), 36.30 (CH_2), 21.96 (CH_3), 19.54 (CH_3)

IR (HATR): 3486, 2971, 1682 (s), 1631, 1372, 1274 (s), 1229, 1197, 1133, 1101, 1068, 993, 972, 904, 862, 774, 758 cm^{-1}

NMR-data of the migration product 2.84



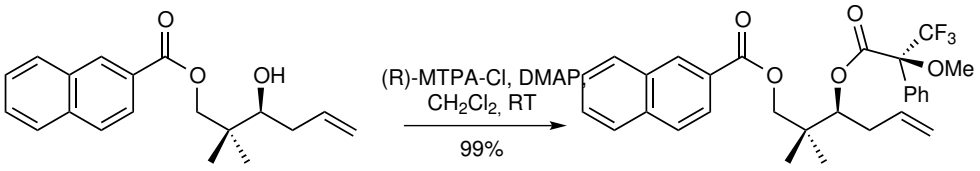
2.84

Name: (3*S*)-1-hydroxy-2,2-dimethylhex-5-en-3-yl 2'-naphthoate

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 8.61 (d, J = 1.6 Hz, 1H), 8.05 (dd, J = 8.7, 1.8 Hz, 1H), 7.97 (app. dd, J = 8.2, 0.9 Hz, 1H), 7.91-7.87 (m, 2H), 7.61 (ddd, J = 8.2, 6.8, 1.4 Hz, 1H), 7.56 (ddd, J = 8.1, 6.8, 1.3 Hz, 1H), 5.81 (app. ddt, J = 17.0, 10.2, 6.9 Hz, 1H), 5.27 (dd, J = 8.5, 4.6 Hz, 1H), 5.13 (ddd, J = 17.0, 3.2, 1.5 Hz, 1H), 5.01-4.97 (m, 1H), 3.43 (d, J = 11.8 Hz, 1H), 3.20 (d, J = 11.6 Hz, 1H), 2.54-2.50 (m, 2H), 1.11 (s, 3H), 0.97 (s, 3H)

APT (125 MHz; aceton$-d_6$): δ (ppm) = 167.78 (C), 135.83 (C), 134.80 (CH), 132.63 (C), 131.48 (CH), 129.55 (CH), 128.57 (CH), 128.41 (CH), 127.93 (CH), 127.18 (C), 126.88 (CH), 125.39 (CH), 117.81 (CH_2), 77.21 (CH), 69.44 (CH_2), 39.84 (C), 34.04 (CH_2), 22.28 (CH_3), 19.00 (CH_3)

5.6.4 Synthesis of (*R*)-MTPA ester 2.86



2.83 **2.86**

To a solution of **2.83** (10 mg, 33 μmol, 1 eq.) and 4-(*N,N*-dimethylamino)pyridine (DMAP) (16 mg, 134 μmol, 4 eq.) in CH_2Cl_2 (335 μl) was added (*R*)-(-)-α-methoxy-α-trifluoromethylphenylacetylchloride ((*R*)-MTPA-Cl) (13 μl, 67 μmol,

2 eq.) at RT. After 19h of stirring at RT, TLC-analysis (hexane/ EtOAc 8/2) indicated complete consumption of the starting material, and the reaction mixture was poured in an aqueous saturated NH_4Cl solution (5 ml) and extracted with CH_2Cl_2 (3 x 5 ml). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (hexane/ EtOAc 95/5) delivered **2.87** (17 mg, 32 μmol, 99%) as a clear oil.

Name: (*3S*)-2,2-dimethyl-3-(((2"*S*)-3",3",3"-trifluoro-2"-methoxy-2"-phenylpropanoyl)oxy)hex-5-en-1-yl 2'-naphthoate

Formula: $C_{29}H_{29}F_3O_5$

Molecular weight: 514.5 g/mol

R_f: 0.17 (hexane/ EtOAc 95/5)

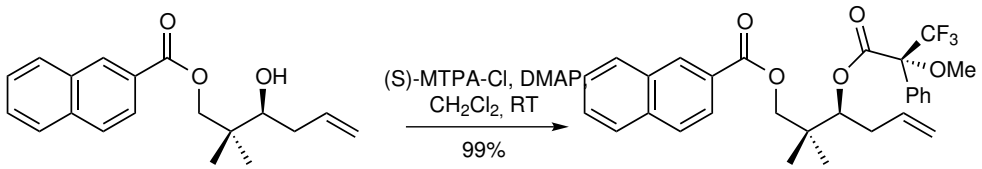
ESI-MS (m/z): 532.2 ($M+NH_4^+$)

HR-MS: calculated for ($M+NH_4^+$) 532.2305, found 532.2300 (Δ 1.0 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 8.63 (app. d, J = 1.7 Hz, 1H), 8.07 (dd, J = 8.6, 1.7 Hz, 1H), 7.99 (app. dd, J = 8.1, 0.7 Hz, 1H), 7.92-7.87 (m, 2H), 7.60 (ddd, J = 8.2, 6.8, 1.4 Hz, 1H), 7.58-7.51 (m, 3H), 7.40-7.31 (m, 3H), 5.78 (dddd, J = 17.0, 10.1, 8.3, 5.7 Hz, 1H), 5.42 (dd, J = 9.5, 3.1 Hz, 1H), 5.07 (ddd, J = 17.0, 3.0, 1.7 Hz, 1H), 5.02 (ddd, J = 10.1, 2.4, 1.6 Hz, 1H), 4.24 (d, J = 11.1 Hz, 1H), 3.97 (d, J = 11.1 Hz, 1H), 3.47 (s, 3H), 2.58 (app. dddt, J = 14.8, 5.8, 3.1, 1.6 Hz, 1H), 2.40 (app. dddt, J = 14.8, 9.5, 8.4, 1.0 Hz, 1H), 1.10 (s, 3H), 1.07 (s, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 166.60 (C), 166.18 (C), 135.74 (C), 134.21 (CH), 132.66 (C), 131.79 (C), 131.37 (CH), 129.76 (CH), 129.66 (CH), 128.54 (3 x CH), 128.49 (CH), 128.46 (CH), 128.00 (CH), 127.90 (CH), 127.33 (C), 126.82 (CH), 125.28 (CH), 123.59 (q, 2 J(C-F_3) = 289 Hz, C), 118.32 (CH2), 85.00 (q, J = 3 J(C-F_3) = 27.6 Hz, C), 79.25 (CH), 70.10 (CH2), 55.31 (CH3), 38.57 (C), 34.88 (CH2), 21.81 (CH3), 20.77 (CH3)

5.6.5 Synthesis of (*R*)-MTPA ester 2.87



2.83 **2.87**

To a solution of **2.83** (10 mg, 33 μmol, 1 eq.) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (16 mg, 134 μmol, 4 eq.) in CH_2Cl_2 (335 μl) was added (*S*)-(-)-α-methoxy-α-trifluoromethylphenylacetylchloride ((*S*)-MTPA-Cl) (13 μl, 67 μmol, 2 eq.) at RT. After 19h of stirring at RT, TLC-analysis (hexane/ EtOAc 8/2) indicated complete consumption of the starting material, and the reaction mixture was poured in an aqueous saturated NH_4Cl solution (5 ml) and extracted with CH_2Cl_2 (3 x 5 ml). The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (hexane/ EtOAc 95/5) delivered **2.87** (17 mg, 32 μmol, 99%) as a clear oil.

Name: (*3S*)-2,2-dimethyl-3-(((2"*R*)-3",3",3"-trifluoro-2"-methoxy-2"-phenylpropanoyl)oxy)hex-5-en-1-yl 2'-naphthoate

Formula: $C_{29}H_{29}F_3O_5$

Molecular weight: 514.5 g/mol

R_f: 0.17 (hexane/ EtOAc 95/5)

ESI-MS (m/z): 532.2 ($M+NH_4^+$)

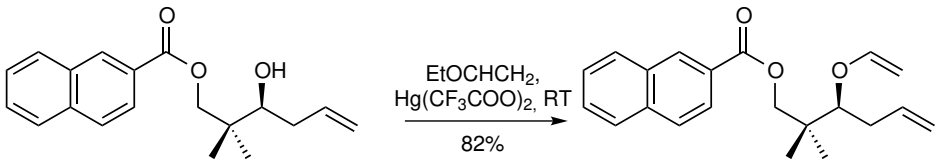
HR-MS: calculated for ($M+NH_4^+$) 532.2305, found 532.2288 (Δ 3.4 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 8.64 (app. d, J = 1.8 Hz, 1H), 8.08 (dd, J = 8.6, 1.7 Hz, 1H), 8.00 (app. dd, J = 8.1, 0.8 Hz, 1H), 7.93-7.88 (m, 2H), 7.61 (ddd, J = 8.2, 6.8, 1.4 Hz, 1H), 7.58-7.54 (m, 3H), 7.39-7.29 (m, 3H), 5.84 (dddd, J = 17.0, 10.1, 8.3, 5.4 Hz, 1H), 5.47 (dd, J = 9.7, 3.0 Hz,

1H), 5.11 (app. ddd, J = 17.0, 3.0, 1.8 Hz, 1H), 5.08 (app. dtd, 10.2, 1.7, 0.9 Hz, 1H), 4.19 (d, 11.1 Hz, 1H), 3.89 (d, 11.1 Hz, 1H), 3.56 (s, 3H), 2.62 (app. dddt, J = 15.0, 5.4, 3.1, 1.7 Hz, 1H), 2.44 (app. dddt, J = 15.0, 9.6, 8.5, 1.1 Hz, 1H), 1.06 (s, 3H), 1.05 (s, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 166.53 (C), 166.15 (C), 135.75 (C), 134.56 (CH) 132.66 (C), 132.22 (C), 131.36 (CH), 129.69 (CH), 129.64 (CH), 128.51 (CH), 128.47 (CH), 128.39 (3 x CH), 127.91 (CH), 127.57 (CH), 127.36 (C), 126.84 (CH), 125.28 (CH), 123.55 (q, 2 J(C-F_3) = 289 Hz, C), 118.31 (CH_2), 84.55 (q, J = 3 J(C-F_3) = 27.6 Hz, C), 79.19 (CH), 69.96 (CH_2), 55.67 (CH_3), 38.64 (C), 34.97 (CH_2), 21.83 (CH_3), 20.60 (CH_3)

5.6.6 Synthesis of enol ether 2.85



2.83 **2.85**

To a solution of alcohol **2.83** (668 mg, 2.24 mmol, 1 eq.) in ethyl vinylether (34 ml) was added mercury(II)trifluoroacetate (191 mg, 0.45 mmol, 0.2 eq.) and the reaction mixture was stirred for 3 days at room temperature. A saturated aqueous solution of $NaHCO_3$ (25 ml) was added to the mixture, the phases were separated and the aqueous one was extracted with Et_2O (3 x 30 ml). The combined organic phases were dried over $MgSO_4$, concentrated and subjected to flash column chromatography (pentane/ Et_2O 95/5) to yield enol ether **2.85** (596 mg, 1.83 mmol, 82%) as a yellowish oil.

Name: ((3*S*)-2,2-dimethyl-3-(vinyloxy)hex-5-en-1-yl 2'-naphthoate

Formula: $C_{21}H_{24}O_3$

Molecular weight: 324.4 g/mol

R_f: 0.39 (pentane/ Et_2O 95/5)

ESI-MS (m/z): 325.2 ($M+H^+$)

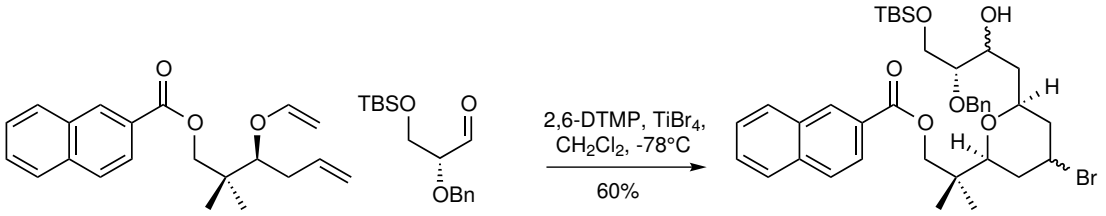
HR-MS: calculated for ($M+H^+$) 325.1798, found 325.1799 (Δ 0.3 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 8.60 (d, J = 1.6 Hz, 1H), 8.05 (dd, J = 8.6, 1.8 Hz, 1H), 7.97 (app. dd, J = 8.0, 0.8 Hz, 1H), 7.92-7.87 (m, 2H), 7.60 (ddd, J = 8.2, 6.8, 1.4 Hz, 1H), 7.56 ddd, J = 8.1, 6.8, 1.4 Hz, 1H), 6.30 (dd, J = 13.9, 6.4 Hz, 1H), 5.90 (app. ddt, J = 17.1, 10.1, 7.0 Hz, 1H), 5.13 (ddd, J = 17.1, 3.3, 1.6 Hz, 1H), 5.08 (app. ddt, J = 10.1, 2.1, 1.1 Hz, 1H), 4.31 (dd, J = 13.9, 1.6 Hz, 1H), 4.25 (d, J = 10.9 Hz, 1H), 4.20 (d, J = 10.9 Hz, 1H), 3.89 (dd, J = 6.4, 1.5 Hz, 1H), 3.78 (dd, J = 8.5, 4.0 Hz, 1H), 2.46-2.35 (m, 2H), 1.11 (s, 3H), 1.10 (s, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 166.67 (C), 153.71 (CH), 135.69 (CH+C), 132.65 (C), 131.13 (CH), 129.51 (CH), 128.43 (CH), 128.39 (CH), 127.93 (CH), 127.72 (C), 126.94 (CH), 125.26 (CH), 117.33 (CH_2), 87.74 (CH_2), 85.27 (CH), 70.69 (CH_2), 39.48 (C), 35.14 (CH_2), 22.07 (CH_3), 20.54 (CH_3)

5.7 Second attempt on the MAP reaction and proof of stereochemistry

5.7.1 Synthesis of THP ether 2.89



2.85 **2.4** **2.89**

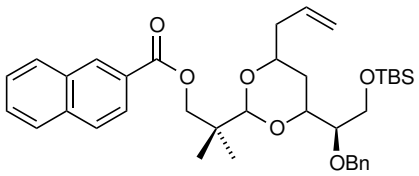
To a solution of enol ether **2.85** (274 mg, 0.84 mmol, 1 eq.), aldehyde **2.4** (528 mg, 1.79 mmol, 2.1 eq.) and 2,6-di-t-butyl-4-methyl-pyridine (289 mg, 1.41 mmol, 1.7 eq.) in CH_2Cl_2 (5 ml), was added $TiBr_4$ (5.2 ml, 1.7 mmol, 0.34 M, 2 eq.) at -78°C. The reaction mixture was stirred for 2h, after which TLC-analysis (hexane/ EtOAc 8/2) showed full conversion of the enol ether. The reaction was quenched by the careful addition of a saturated aqueous solution of $NaHCO_3$ (25 ml), and diluted with CH_2Cl_2 (20 ml). The layers were separated, and the aqueous one was extracted with CH_2Cl_2 (3 x 25 ml). The combined organic phases were dried over MgSO4, concentrated and subjected to flash column chromatography (hexane/ EtOAc 9/1), resulting isolation of THP-ether **2.89** (353 mg, 0.55 mmol, 60%) as a mixture of diastereomers. Also, the oxonia-Cope rearrangement product could be isolated (0.06 mmol, 7%).

Formula: $C_{37}H_{51}BrO_6Si$

Molecular weight: 699.8 g/mol

R_f: 0.26-0.31 (hexane/ EtOAc 8/2)

The 2-oxonia cope rearrangement product 2.90



2.90

Formula: $C_{37}H_{50}O_6Si$

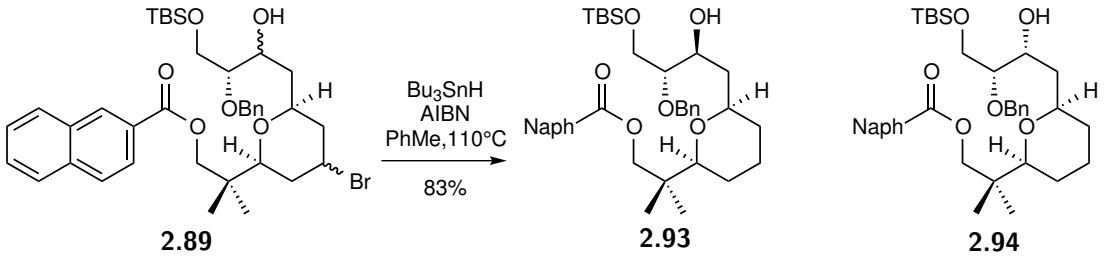
Molecular weight: 618.9 g/mol

R_f: 0.56 (hexane/ EtOAc 8/2)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 8.60 (app. bs, 1H), 8.07 (dd, J = 8.6, 1.6 Hz, 1H), 7.97 (app. d, J = 7.9 Hz, 1H), 7.91-7.85 (m, 2H), 7.62-7.52 (m, 2H), 7.38-7.24 (m, 5H), 5.81 (app. ddt, J = 17.1, 10.0, 7.0 Hz, 1H), 5.06 (ddd, J = 17.3, 2.1, 1.5 Hz, 1H), 5.03 (ddd, J = 10.2, 2.2, 1.1 Hz, 1H), 4.75 (d, J = 11.9 Hz, 1H, A part of AB-spinsystem), 4.69 (d, J = 11.9 Hz, 1H, B part of AB-spinsystem), 4.48 (s, 1H), 4.32 (d, J = 10.7 Hz, 1H, A part of AB-sinsytem), 4.25 (d, J = 10.7 Hz, 1H, B part of AB-spinsystem), 3.86-3.79 (m, 2H), 3.71 (dd, J = 10.8, 5.7 Hz, 1H), 3.64-3.58 (m, 1H), 3.50-3.45 (m, 1H), 2.37-2.28 (m, 1H), 2.24-2.16 (m, 1H), 1.49 (app. dt, J = 13.0, 2.5 Hz, 1H), 1.38 (app. dt, J = 13.0, 11.2 Hz, 1H), 1.13 (s, 3H), 1.12 (s, 3H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 166.85 (C), 139.07 (C), 135.63 (C), 134.25 (CH), 132.68 (C), 131.06 (CH), 129.51 (CH), 128.38 (2 x CH), 128.28 (CH), 128.25 (CH), 128.07 (C), 127.93 (2 x CH), 127.92 (CH), 127.58 (CH), 126.73 (CH), 125.44 (CH), 117.21 (CH_2), 104.11 (CH), 81.77 (CH), 77.16 (CH), 75.83 (CH), 73.38 (CH_2), 70.29 (CH), 62.79 (CH_2), 40.48 (CH2), 39.27 (C), 32.18 (CH_2), 26.06 (3 x CH_3), 20.44 (CH_3), 20.01 (CH_3), 18.39 (C), -5.26 (2 x CH_3)

5.7.2 Synthesis of debrominated THP ethers 2.93 and 2.94



2.89 **2.93** **2.94**

To a solution of bromide **2.89** (10 mg, 14 μmol, 1 eq.) and tributyltin hydride (21 μl, 21μ, 1M in cyclohexane, 1.5 eq.) in toluene (570 μl) was added AIBN (spatula tip, 0.05 eq.). The pressure tube was sealed, heated to 110°C, and stirred for 2h. Then, the reaction mixture was poured in water (10 ml) and extracted with CH_2Cl_2 (3 x 10 ml). The combined organic layers were dried over $MgSO_4$ and concentrated. The residu was purified by flash column chromatography (CH_2Cl_2/ Et_2O 99/1), resulting in 2 diastereomers, a less polar one, (3.6 mg, 5.8 μmol, 41%) and a more polar one (3.5 mg, 5.6 μmol, 40%). The absolute configuration of the alcohol was not established.

Formula: $C_{37}H_{52}O_6Si$

Molecular weight: 620.9 g/mol

More apolar isomer

R_f: 0.30 (CH_2Cl_2/ Et_2O 98/2)

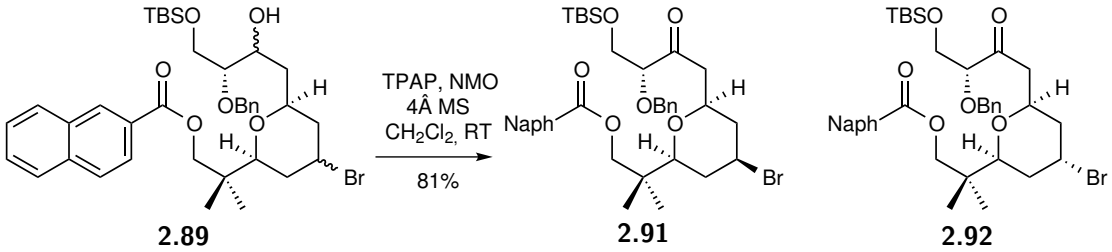
^{1}H-NMR (300 MHz; $CDCl_3$): δ (ppm) = 8.60 (app. bs, 1H), 8.06 (app. dd, J = 8.6, 1.7 Hz, 1H), 7.99-7.94 (m, 1H), 8.72 (app. d, J = 8.7 Hz, 2H), 7.63-7.51 (m, 2H), 7.37-7.22 (m, 5H), 4.74 (d, J = 11.9, 1H, A part of AB-spinsystem), 4.63 (d, J = 11.7, 1H, B part of AB-spinsystem), 4.44 (d, J = 10.7 HZ, 1H), 4.12-4.03 (m, 2H), 3.86 (dd, J = 10.9, 4.3 Hz, 1H), 3.78 (dd, J = 10.8, 5.8 HZ, 1H), 3.60-3.50 (m, 1H), 3.43 (app. td, J = 5.6, 4.4 Hz, 1H), 3.27-3.19 (m, 2H), 1.92-1.82 (m, 1H), 1.71-1.22 (m, 7H), 1.04 (s, 3H), 1.03 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H)

More polar isomer

R_f: 0.28 (CH_2Cl_2/ Et_2O 98/2)

^{1}H-NMR (300 MHz; $CDCl_3$): δ (ppm) = 8.59 (app. bs, 1H), 8.06 (app. dd, J = 8.6, 1.7Hz, 1H), 8.00-7.95 (m, 1H), 7.89 (app. d, J = 8.5 Hz, 2H), 7.63-7.51 (m, 2H), 7.35-7.23 (m, 5H), 4.75 (d, J = 11.7 HZ, 1H, A part of AB-spinsystem), 4.55 (d, J = 11.9 Hz, 1H, B part of AB-spinsystem), 4.22 (d, J = 10.9 Hz, 1H, A part of AB-spinsystem), 4.19 (d, J = 10.9 Hz, 1H, B part of AB-spinsystem), 4-3.92 (m, 1H), 3.88 (dd, J = 10.8, 4.3 HZ, 1H), 3.77 (dd, J = 10.7, 5.8 Hz, 1H), 3.47-3/37 (m, 2H), 3.31-3.24 (m, 2H), 1.92-1.82 (m, 1H), 1.80-1.16 (m, 7H), 1.06 (s, 3H), 1.03 (s, 3H), 0.89 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H)

5.7.3 Synthesis of ketones 2.91 and 2.92



To a suspension of alcohol **2.89** (400 mg, 0.57 mmol, 1 eq.), N-methyl morpholine N-oxide (NMO) (200 mg, 1.71 mmol, 3 eq.), and molecular sieves (4 Å) (375 mg) in CH_2Cl_2 (15 ml) was added tetrapropyl ammonium perruthenate (TPAP) (10 mg, 0.03 mmol, 0.05 eq.) in one portion. The reaction mixture was stirred for 3h at room temperature, after which it was filtered over a P4 filter. The filtrate was concentrated and purified by consecutive flash column chromatography (hexane/ EtOAc 9/1) to yield **2.91** (159 mg, 0.23 mmol, 40%) and **2.92** (161 mg, 0.24 mmol, 41%).

Formula: $C_{37}H_{49}BrO_6Si$

Molecular weight: 697.8 g/mol

More apolar isomer (equatoral bromide, 2.91)

Name: 2-((2"*S*,4"*R*,6"*S*)-6"-((*R*)-3"'-(benzyloxy)-4"'-((tert-butyldimethylsilyl)-oxy)-2"'-oxobutyl)-4"-bromotetrahydro-2H-pyran-2"-yl)-2-methylpropyl 2'-naphthoate

R_f: 0.62 (hexane/ EtOAc 8/2)

ESI-MS (m/z): 714.3 ($M+NH_4^+$)

^{1}H-NMR (300 MHz; $CDCl_3$): δ (ppm) = 8.58 (app. d, J = 1.6 Hz, 1H), 8.04 (dd, J = 8.6, 1.7 Hz, 1H), 7.98 (app. dd, J = 8.0, 0.8 Hz, 1H), 7.90-7.87 (m, 2H), 7.60 (ddd, J = 8.2, 6.8, 1.4 Hz, 1H), 7.55 (ddd, J = 8.1, 6.8, 1.3 Hz, 1H), 7.36-7.27 (m, 5H), 4.61 (d, J = 11.9 Hz, 1H, A part of AB-spinsystem), 4.57 (d, J = 11.9 Hz, 1H, B part of AB-spinsystem), 4.23-4.14 (m, 1H), 4.21 (d, J = 10.8 Hz, 1H, A part of AB-spinsystem), 4.16 (d, J = 10.8 Hz, 1H, B part of AB-spinsystem), 3.91-3.79 (m, 4H), 3.30 (dd, J = 11.4, 1.7 Hz, 1H), 2.91 (dd, J = 17.5, 6.5 Hz, 1H), 2.62 (dd, J = 17.5, 6.0 Hz, 1H), 2.33-2.27 (m, 2H), 1.85 (app. dt, J = 12.8, 11.7 Hz, 1H), 1.65 (ddd, J = 12.8, 12.1, 11.0 Hz, 1H), 1.03 (s, 3H), 1.02 (s, 3H), 0.84 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H)

APT (75 MHz; $CDCl_3$): δ (ppm) = 208.43 (C), 166.71 (C), 137.72 (C), 135.68 (C), 132.67 (C), 131.11 (CH), 129.55 (CH), 128.61 (2 x CH), 128.39 (CH), 128.37 (CH), 128.05 (CH), 127.98 (2 x CH), 127.92 (CH), 127.77 (C), 126.81 (CH), 125.33 (CH), 85.54 (CH), 81.76 (CH), 73.56 (CH), 72.71 (CH_2), 70.38 (CH_2), 63.98 (CH_2), 47.11 (CH), 45.78 (CH_2), 43.14 (CH_2), 38.32 (C), 37.58 (CH_2), 25.95 (3 x CH_3), 21.71 (CH_3), 20.45 (CH_3), -5.34 (CH_3), -5.36 (CH_3)

More polar isomer (axial bromide, 2.92)

Name: 2-((2"*S*,4"*S*,6"*S*)-6"-((*R*)-3"'-(benzyloxy)-4"'-((tert-butyldimethylsilyl)-oxy)-2"'-oxobutyl)-4"-bromotetrahydro-2H-pyran-2"-yl)-2-methylpropyl 2'-naphthoate

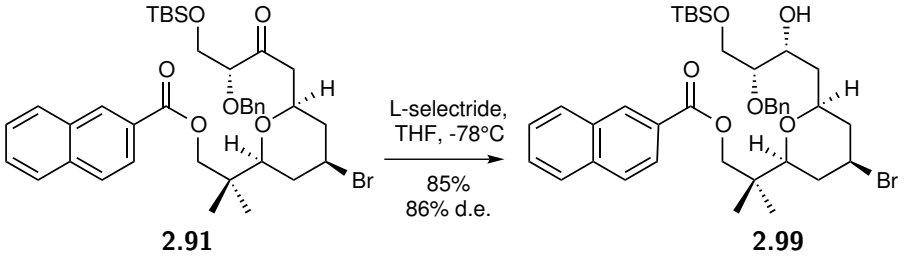
R_f: 0.52 (hexane/ EtOAc 8/2)

ESI-MS (m/z): 714.3 ($M+NH_4^+$)

^{1}H-NMR (300 MHz; $CDCl_3$): δ (ppm) = 8.62 (app. d, J = 1.7 Hz, 1H), 8.07 (dd, J = 8.7, 1.9 Hz, 1H), 7.96 (app. dd, J = 8.1, 0.8 Hz, 1H), 7.90-7.86 (m, 2H), 7.59 (ddd, J = 8.2, 6.8, 1.4 Hz, 1H), 7.54 (ddd, J = 8.1, 6.8, 1.3 Hz, 1H), 7.39-7.26 (m, 5H), 4.79 (app. quint. J = 3.0 Hz, 1H), 4.63 (d, J = 11.9 Hz, 1H, A part of AB-spinsystem), 4.57 (d, J = 11.9 Hz, 1H, B part of AB-spinsystem), 4.47-4.41 (m, 1H), 4.21 (d, J = 10.8 Hz, 1H, A part of AB-spinsystem), 4.14 (d, J = 10.7 Hz, 1H, B part of AB-spinsystem), 3.96 (dd, J = 11.2, 1.6 Hz, 1H), 3.92 (dd, J = 5.3, 4.3 Hz, 1H), 3.86 (app. d, J = 4.6 Hz, 2H), 2.88 (dd, J = 16.8, 7.5 Hz, 1H), 2.57 (dd, J = 16.8, 5.1 Hz, 1H), 2.07-2.00 (m, 2H), 1.87 (ddd, J = 14.4, 11.1, 3.3 Hz, 1H), 1.72 (ddd, J = 14.5, 11.0, 3.5 Hz, 1H), 1.04 (s, 3H), 1.01 (s, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H)

APT (75 MHz; $CDCl_3$): δ (ppm) = 208.36 (C), 166.79 (C), 137.85 (C), 135.68 (C), 132.69 (C), 131.21 (CH), 129.58 (CH), 128.57 (2 x CH), 128.34 (2 x CH), 127.95 (2 x CH), 127.90 (2 x CH), 127.82 (C), 126.77 (CH), 125.41 (CH), 85.78 (CH), 76.57 (CH), 72.73 (CH_2), 70.45 (CH_2), 69.15 (CH), 64.04 (CH_2), 50.72 (CH), 45.60 (CH_2), 39.48 (CH_2), 37.81 (C), 33.62 (CH_2), 25.97 (3 x CH_3), 21.40 (CH_3), 21.04 (CH_3), -5.32 (2 x CH_3)

5.7.4 Synthesis of alcohol 2.99



2.91 **2.99**

To a solution of ketone **2.91** (20 mg, 28 μmol, 1. eq.) in THF (0.4 ml) was

added L-selectride (143 μl, 143 μmol, 1M in THF, 5 eq.) at -78°C. After 2 hours of stirring at that temperature, the reaction was quenched by the addition of water (5 ml) and diluted with EtOAc (5 ml). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 5 ml). The combined organic phases were dried over MgSO4, concentrated and subjected to flash column chromatography (hexane/ EtOAc 8/2), delivering **2.99** (17 mg, 24 μmol, 85%) as a sticky oil.

Name: 2-((2"*S*,4"*R*,6"*S*)-6"-((2"'*R*,3"'*R*)-3"'-(benzyloxy)-4"'-((tert-butyldimethylsilyl)oxy)-2"'-hydroxybutyl)-4"-bromotetrahydro-2H-pyran-2-yl)-2-methylpropyl 2'-naphthoate

Formula: $C_{37}H_{51}BrO_6Si$

Molecular weight: 699.8 g/mol

R_f: 0.50 (hexane/ EtOAc 8/2)

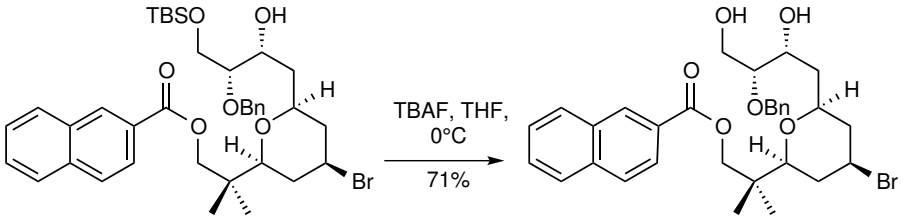
ESI-MS (m/z): 699.3 ($M+H^+$)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 8.58 (app. bs, 1H), 8.04 (dd, J = 8.6, 1.7 Hz, 1H), 7.98 (app. d, J = 8.0 Hz, 1H), 7.92-7.88 (m, 2H), 7.61 (ddd, J = 8.2, 6.9, 1.3 Hz, 1H), 7.56 (ddd, J = 8.0, 6.9, 1.3 Hz, 1H), 7.35-7.25 (m, 5H), 4.73 (d, J = 11.8 Hz, 1H, A part of AB-spinsystem), 4.48 (d, J = 11.8 Hz, 1H, B part of AB-spinsystem), 4.26 (d, J = 10.8 Hz, 1H, A part of AB-spinsystem), 4.14 (d, J = 10.7 Hz, 1H, B part of AB-spinsystem), 4.09 (app. tt, J = 12.0, 4.3 Hz, 1H), 3.93-3.88 (m, 1H), 3.85 (dd, J = 10.8, 4.6 Hz, 1H), 3.77 (dd, J = 10.8, 5.2 Hz, 1H), 3.36 (app. dd, J = 8.8, 4.7 Hz, 1H), 3.32-3.26 (m, 1H), 3.23 (dd, J = 11.3, 1.5 Hz, 1H), 2.96 (bs, 1H), 2.32-2.26 (m, 1H), 2.19-2.13 (m, 1H), 1.85 (dd, J = 24, 13 Hz, 1H), 1.79 (app.dt, J = 14.2, 8.2 Hz, 1H), 1.69 (dd, J = 23.8, 12.3 Hz, 1H), 1.62 (app. dt, J = 14.2, 4.7 Hz, 1H), 1.05 (s, 6H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 166.65 (C), 138.55 (C), 135.70 (C), 132.66 (C), 131.14 (CH), 129.52 (CH), 128.50 (2 x CH), 128.47 (CH), 128.40 (CH) ,

128.34 (2 x CH), 127.94 (CH), 127.90 (CH), 127.68 (C), 126.89 (CH), 125.29 (CH), 81.71 (CH), 80.21 (CH), 76.18 (CH), 72.69 (CH2), 70.47 (CH2), 69.64 (CH), 63.13 (CH_2), 47.34 (CH), 43.36 (CH_2), 38.77 (CH_2), 38.32 (CH_2), 37.70 (CH_2), 26.03 (3 x CH_3), 21.81 (CH3), 20.59 (CH_3), 18.38 (C), -5.33 (2 x CH_3)

5.7.5 Synthesis of diol 2.101



2.99 **2.101**

To a solution of alcohol **2.99** (17 mg, 24 μmol, 1 eq.) in THF (100 μl) was added TBAF (36 μl, 36 μmol, 1.5 eq.) at 0C. The reaction was stirred at that temperature for 1h. TLC-analysis (hexane/ EtOAc 6/4) after 25' indicated full conversion. The reaction was quenched by the addition of water (5ml) and diluted with EtOAc (5 ml). The phases were separated and the aqueous one was extracted with Et_2O (3 x 5 ml). The combined organic extracts were dried over MgSO4 and concentrated, delivering diol **2.101** (10 mg, 17 μmol, 71%) as a solid, which was used as such in the next reaction.

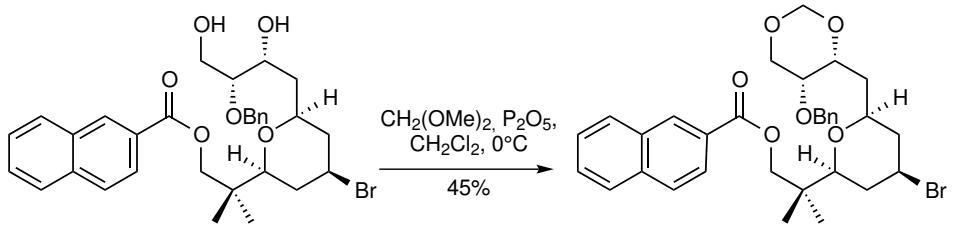
Name: 2-((2"*S*,4"*R*,6"*S*)-6"-((2"'*R*,3"'*R*)-3"'-(benzyloxy)-2"',4"'-dihydroxybutyl)-4"-bromotetrahydro-2H-pyran-2"-yl)-2-methylpropyl 2'-naphthoate

Formula: $C_{31}H_{37}BrO_6$

Molecular weight: 585.5 g/mol

R_f: 0.18 (hexane/ EtOAc 6/4)

5.7.6 Synthesis of acetal 2.102



2.101 **2.102**

To a solution of diol **2.101** (9 mg, 15 μmol, 1 eq.), and dimethoxymethane (320 μl, 3.61 mmol, 240 eq.) in CH_2Cl_2 (1.8 ml), was added phosphorous pentoxide (90 mg, 600 μmol, 40 eq.) at 0C. The reaction was quenched by the addition of a saturated aqueous solution of $NaHCO_3$ (1ml) and extracted with Et_2O (3 x 3 ml). The combined organic layers were dried over $MgSO_4$, concentrated and subjected to flash column chromatography (hexane/ EtOAc 8/2), delivering acetal **2.102** (4 mg, 7 μmol, 45%) as yellowish oil.

Name: 2-((2"*S*,4"*R*,6"*S*)-6"-(((4"'*R*,5"'*R*)-5"'-(benzyloxy)-1"',3"'-dioxan-4"'-yl)-methyl)-4"-bromotetrahydro-2H-pyran-2"-yl)-2-methylpropyl 2'-naphthoate

Formula: $C_{32}H_{37}BrO_6$

Molecular weight: 597.6 g/mol

R_f: 0.26 (hexane/ EtOAc 8/2)

ESI-MS (m/z): 614.2 ($M+NH_4^+$)

HR-MS: calculated for ($M+NH_4^+$) 614.2112, found 614.2108 (Δ 0.6 ppm)

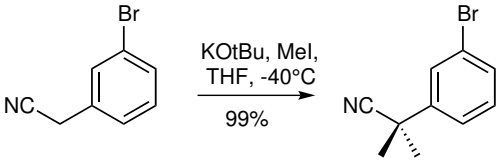
^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 8.58 (app. bs, 1H), 8.04 (dd, J = 8.6, 1.6 Hz, 1H), 8.02 (app. d, J = 8.0 Hz, 1H), 7.97-7.92 (m, 2H), 7.67-7.58 (m, 2H), 7.26-7.22 (m, 1H), 7.19-7.14 (m, 2H), 6.93-6.90 (m, 2H), 5.07 (d, J = 6.1 Hz, 1H), 5.76 (d, J = 6.1 Hz, 1H), 4.56 (d, J = 12.4 Hz, 1H, A part of AB-spinstem 1), 4.47 (d, J = 10.5 Hz, 1H, A part of AB-spinsystem 2), 4.11 (app.d, J = 13.4 Hz, 1H), 3.91 (d, J = 12.5 Hz, 1H, B part of AB-spinsystem

1), 3.83 (ddd, J = 9.9, 5.1, 1.7 Hz, 1H), 3.77 (d, J = 10.5 Hz, 1H, B part of AB-spinsystem 2), 3.77-3.70, (m, 1H), 3.73 (dd, J = 12.5, 1.3 Hz, 1H), 2.87 (dd, J = 11.4, 1.8 Hz, 1H), 2.85 (app. td, J = 1.7, 0.5 Hz, 1H), 2.39-2.32 (m, 1H), 2.17-2.13 (m, 1H), 1.90-1.85 (m, 1H), 1.80 (ddd, J = 13.4, 10.0, 3.2 Hz, 1H), 1.72-1.64 (m, 2H), 1.58-1.52 (m, 1H), 1.07 (s, 3H), 0.96 (s, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 166.47 (C), 137.88 (C), 135.76 (C), 132.68 (C), 131.04 (CH), 129.45 (CH), 128.80 (2 x CH), 128.77 (CH), 128.61 (CH), 128.39 (2 x CH), 128.05 (CH), 127.99 (CH), 127.55 (C), 127.20 (CH), 125.08 (CH), 94.02 (CH_2), 80.25 (CH), 75.20 (CH), 72.95 (CH), 70.64 (CH_2), 70.46 (CH_2), 69.52 (CH), 67.06 (CH_2), 47.15 (CH), 43.33 (CH_2), 38.05 (C), 37.23 (CH_2), 36.12 (CH_2), 29.85 (CH_2), 22.35 (CH_3), 19.23 (CH_3)

5.8 Synthesis of the C_5-C_{12} fragment of pelofen

5.8.1 Synthesis of nitrile 3.13



3.12 **3.13**

To a stirring solution of 3'-bromophenylacetonitrile (**3.12**) (22.15 g, 113 mmol) in THF (330 ml) at -40°C was added KO*t*-Bu (27.90 g, 249 mmol) and the mixture was stirred for 10'. After dropwise addition of MeI (17.6 ml, 283mmol) the cooling bath was removed and the resulting pink milk was stirred at RT. TLC-analysis (micro-extraction 1M HCl/Et_2O; pentane/Et_2O 9/1) indicated completion of the reaction after 2.5h. 1M HCl solution (50 ml) was added reaction mixture and the resulting yellow mixture was poured in H_2O (150 ml), followed by extraction (3 x 200 ml EtOAc). The combined organic fractions were washed with a mixture of a saturated aqueous $NaHCO_3$ solution and brine 2/1 (300 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting brown oil was purified by flash column chromatography (pentane/Et_2O 9/1) to give **3.13** (25.05 g, 99% yield) as a clear, yellow oil.

Name: 2-(3'-Bromophenyl)-2-methylpropanenitrile

Formula: $C_{10}H_{10}BrN$

Molecular weight: 224.1 g/mol

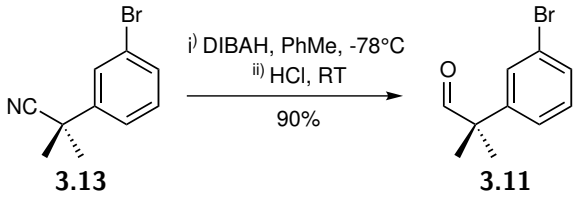
R_f: 0.42 (pentane/Et_2O 8/2)

^{1}H-NMR (300 MHz; aceton$-d_6$): δ (ppm) = 7.71 (1H, s), 7.58-7.52 (2H, m (app. t)), 7.41-7.36 (1H, m), 1.74 (6H, s)

APT (75 MHz; aceton$-d_6$): δ (ppm) = 145.47 (C), 131.80 (CH), 131.74 (CH), 129.12 (CH), 125.21 (CH), 124.65 (C), 123.33 (C), 37.88 (C), 29.02 (2 x CH_3)

IR (HATR): 3066 (w), 2982, 2937, 2875 (w), 2237, 1594, 1566, 1476, 1418, 1392, 1369, 1274 (w), 1239, 1198, 1176 (w), 1114, 1091, 1074, 997, 934, 879, 847, 784 (s), 722, 692 (s), 657 cm^{-1}

5.8.2 Synthesis of aldehyde 3.11



3.13 **3.11**

To a stirring solution of **3.13** (1.50 g, 6.69 mmol, 1eq.) in toluene (10.7 ml) at -50°C was added DIBAL-H (6.75 ml, 10.04 mmol, 25 w% in PhMe, 1.5 eq.) dropwise over an hour, using a syringe pump. After the addition, the mixture was stirred for 2 h at the same temperature, upon which TLC-analysis (pentane/Et_2O 9/1) showed complete conversion of the starting material. 6M HCl (20.1 ml) was added, the cooling bath was removed and the mixture was stirred for 1h. The mixture was poured in H_2O (10 ml) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (5 x 30 ml) and the combined organic phases were washed with a preformed mixture of a saturated aqueous $NaHCO_3$ solution (15 ml) and saturated aqueous NaCl solution (15 ml). After drying over $MgSO_4$ and concentration, flash column chromatography (pentane
ceEt2O 9/1) provided **3.11** (1.36 g, 90% yield) as a clear yellow oil.

Name: 2-(3'-Bromophenyl)-2-methylpropanal

Formula: $C_{10}H_{11}BrO$

Molecular weight: 227.1 g/mol

R_f: 0.39 (pentane/Et_2O 9/1)

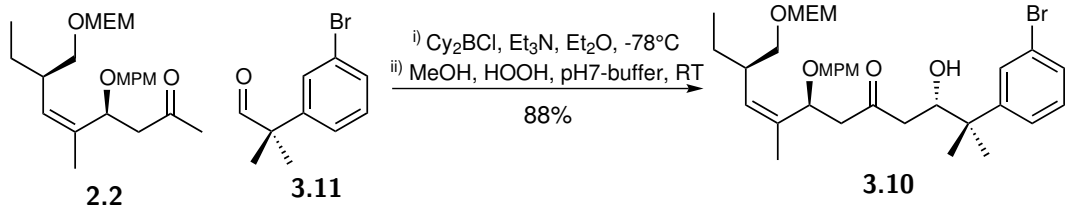
^{1}H-NMR (300 MHz; aceton$-d_6$): δ (ppm) = 9.54 (1H, s), 7.50-7.47 (2H, m), 7.39-7.32 (2H, m), 1.46 (6H, s) ppm

APT (75 MHz; aceton−d_6): δ (ppm) = 202.26 (C), 145.51 (C), 131.53 (CH), 131.01 (CH), 130.62 (CH), 126.75 (CH), 123.38 (C), 50.96 (C), 22.82 (2 x CH_3)

IR (HATR): 3440 (w), 3065 (w), 2973, 2932, 2874 (w), 2807, 2705, 1723 (s), 1592, 1564, 1477, 1409, 1394, 1365, 1305 (w), 1240, 1175 (w), 1113 (w), 1092, 1074, 996, 947 (w), 911, 879, 845, 783, 760, 694 (s), 670 cm^{-1}

5.9 Synthesis of the C_5-C_{20} fragment

5.9.1 Synthesis of hydroxyketone 3.10



To a stirred solution of ketone (1.00 g, 2.45 mmol, 1 eq.) in Et_2O (29 ml) was added triethylamine (580 μl, 4.16 mmol, 1.7 eq.) at RT. The solution was then cooled to 0°C and chlorodicylcohexylborane (3.67 ml, 3.67 mmol, 1.5 eq., 1 M in hexane) was added dropwise, upon which the reaction mixture became turbid. After stirring for 30' at 0°C, the reaction mixture was further cooled to -78°C. A cooled solution of aldehyde (1.69 g, 7.34 mmol, 3eq.) in Et_2O (7 ml) (-20°C) was then added *via* a double-ended needle and the flask containing the aldehyde was rinsed with Et_2O (3 x 1 ml). The reaction mixture was stirred for 15h upon which it was able to warm up to -40°C, after which tlc-analysis showed complete conversion of the starting material (hexane/acetone 8/2). The reaction was quenched by consecutive addition of pH 7 phosphate buffer (26 ml), MeOH (26 ml) and H_2O_2 (4.1 ml, 36.7 mmol, 15 eq., 35 v% in H_2O) and stirred for 3h at RT. The reaction mixture was then poured into a separation funnel containing water (150 ml), extracted with CH_2Cl_2 (4 x 150 ml), dried over $MgSO_4$ and concentrated.

Purification using gradient flash column chromatography (hexane/acetone 95/5 to hexane/acetone 9/1) resulted in hydroxyketone **3.10** as a clear colorless oil (1.37 g, 2.16 mmol, 88%).

Name: (3*S*,7*S*,10*R*,8*Z*)-2-(3'-bromophenyl)-3-hydroxy-7-((4"-methoxybenzyl)oxy)-10-(((2"'-methoxyethoxy)methoxy)methyl)-2,8-dimethyldodec-8-en-5-one

Formula: $C_{33}H_{47}BrO_7$

Molecular weight: 635.6 g/mol

R_f: 0.32 (hexane/acetone 8/2)

$[\alpha]_D$: -11.6° (c = 10 mg/ml in $CHCl_3$)

ESI-MS (m/z): 654.2 ($M+NH_4^+$)

HR-MS: calculated for ($M+Na^+$) 657.2397, found 657.2401 (Δ 0.6 ppm)

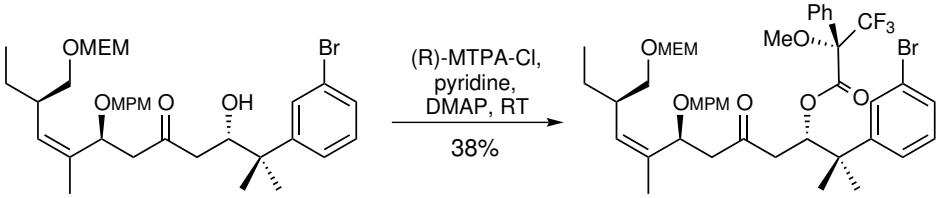
^{1}H-NMR (500 MHz; CD_2Cl_2): δ (ppm) = 7.52 (app. t, J = 1.9 Hz, 1H), 7.34 (ddd, J = 7.8, 2.1, 1.0 Hz, 1H), 7.31 (ddd, J = 8.0, 1.9, 1.0 Hz, 1H), 7.20-7.14 (m, 3H), 6.85 (app. d, 8.7 Hz, 2H), 5.18 (dd, J = 10.5, 1.5 Hz, 1H), 4.72 (dd, J = 10.1, 3.0 Hz, 1H), 4.64 (d, J = 6.6 Hz, 1H, A part of AB-spinsystem), 4.63 (d, J = 6.6 Hz, 1H, B part of AB-spinsystem), 4.31 (d, J = 11.1 Hz, 1H), 4.124 (d, J = 11.1 Hz, 1H), 4.118 (dd, J = 10.5, 1.8 Hz, 1H), 3.79 (s, 3H), 3.63-3.60 (m, 2H), 3.51-3.48 (m, 2H), 3.46 (dd, J = 9.4, 5.8 Hz, 1H), 3.37 (dd, J = 9.4, 7.0 Hz, 1H), 3.31 (s, 3H), 2.85 (dd, J = 15.3, 10.1 Hz, 1H), 2.62-2.53 (m, 1H), 2.43 (dd, J = 17.2, 1.8 Hz, 1H), 2.26 (dd, J = 17.2, 10.4 Hz, 1H), 2.20 (dd, J = 15.3, 3.0 Hz, 1H), 1.69 (d, J = 1.4 Hz, 3H), 1.55-1.45 (m, 1H), 1.28 (s, 3H), 1.26 (s, 3H), 1.20-1.10 (m, 1H), 0.78 (app. t, J = 7.5 Hz, 3H)

APT (125 MHz; CD_2Cl_2): δ (ppm) = 210.22 (C), 159.59 (C), 150.01 (C), 135.28 (C), 132.56 (CH), 131.10 (C), 130.30 (CH), 130.06 (CH), 129.73 (2 x CH), 129.49 (CH), 125.90 (CH), 122.73 (C), 113.99 (2 x CH), 95.84 (CH_2), 74.65

(CH), 73.51 (CH), 72.21 (CH_2), 71.71 (CH_2), 70.15 (CH_2), 67.13 (CH_2), 58.98 (CH_3), 55.61 (CH_3), 48.03 (CH_2), 46.16 (CH_2), 42.16 (C), 39.71 (CH), 25.35 (CH_2), 25.12 (CH_3), 23.66 (CH_3), 17.97 (CH_3), 11.92 (CH_3)

IR (HATR): 3503, 2924, 2357, 1706, 1613, 1514, 1464, 1410, 1248, 1174 cm^{-1}

5.9.2 Synthesis of (*S*)-Mosher ester 3.29



3.10 **3.29**

To a solution of the hydroxy ketone **3.10** (22 mg, 35 μmol, 1 eq.) in pyridine (69 μl) were added (*R*)-MTPA-Cl (12.9 μl, 70 μmol, 2 eq.) and DMAP (0.4 mg, 3.5 μmol, 0.1 eq.) at RT. The reaction was stirred at RT for 20h, after which the mixture was poured in water (10 ml). The mixture was extracted with CH_2Cl_2 (4 x 10 ml), dried over $MgSO_4$ and concentrated. The product was purified by flash column chromatography (pentane/*Et2O* 1/1) and preparative HPLC, yielding **3.29** as a colorless oil (11 mg, 13 μmol, 38%).

Name: (3'*S*,7'*S*,10'*R*,8'*Z*)-2-(3-bromophenyl)-7'-((4"-methoxybenzyl)oxy)-10'-(((2"'-methoxyethoxy)methoxy)methyl)-2',8'-dimethyl-5'-oxododec-8'-en-3'-yl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate

Formula: $C_{43}H_{54}BrF_3O_9$

Molecular weight: 851.8 g/mol

R_f: 0.30 (pentane/Et_2O 1/1)

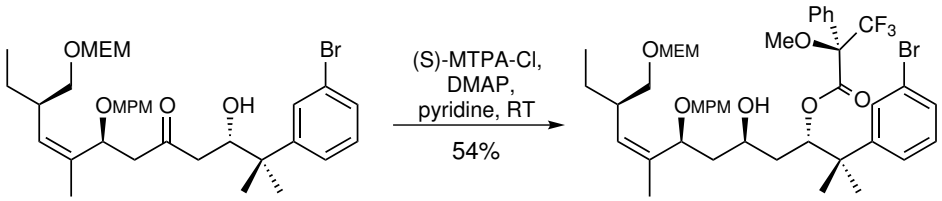
ESI-MS (m/z): 868.2 ($M+NH_4^+$)

HR-MS: calculated for ($M+NH_4^+$) 868.3242, found 868.3235 (Δ 0.8 ppm)

^{1}H-NMR (500 MHz; CD_2Cl_2): δ (ppm) = 7.53 (app.t, J = 1.9 Hz, 1H), 7.42-7.29 (m, 7H), 7.18 (app. t, J = 7.8 Hz, 1H), 7.13 (app. d, J = 8.7 Hz, 2H), 6.84 (app. d, J = 8.7 Hz, 2H), 5.84 (dd, J = 6.0, 5.0 Hz, 1H), 5.18 (app. dd, J = 10.5, 1.5 Hz, 1H), 4.70 (dd, J = 10.3, 2.5 Hz, 1H), 4.64 (d, J = 6.6 Hz, 1H, A part of AB-spinsystem), 4.63 (d, J = 6.6 Hz, 1H, B part of AB-spinsystem), 4.29 (d, J = 10.8 Hz, 1H), 4.11 (d, J = 10.8 Hz, 1H), 3.79 (s, 3H), 3.64-3.60 (m, 2H), 3.51-3.48 (m, 2H), 3.46 (dd, J = 9.5, 5.7 Hz, 1H), 3.39-3.35 (m, 4H), 3.31 (s, 3H), 2.80 (dd, J = 15.5, 10.3 Hz, 1H), 2.61-2.53 (m, 3H), 2.09 (dd, J = 15.5, 2.6 Hz, 1H), 1.66 (d, J = 1.4 Hz, 3H), 1.55-1.45 (m, 1H), 1.28 (s, 3H), 1.25 (s, 3H), 1.19-1.10 (m, 1H), 0.76 (app. t, J = 7.4 Hz, 3H)

APT (125 MHz; CD_2Cl_2): δ (ppm) = 204.93 (C), 165.83 (C), 159.57 (C),148.30 (C), 135.31 (C), 132.49 (CH), 132.09 (C), 131.18 (C), 130.37 (CH), 130.19 (CH), 130.13 (CH), 129.97 (CH), 129.75 (2 x CH), 128.76 (3? x CH), 128.13 (CH), 125.84 (CH), 123.82 (q, J(^{13}C-^{19}F) = 287.9 Hz, C), 122.97 (C), 113.97 (2 x CH), 95.84 (CH_2), 85.01 (app. d, J(^{13}C-^{19}F) = 57.2 Hz, C), 78.48 (CH), 73.56 (CH), 72.22 (CH_2), 71.69 (CH_2), 70.26 (CH_2), 67.13 (CH_2), 58.98 (CH_3), 55.62 (CH_3), 55.44 (CH_3), 47.70 (CH_2), 45.30 (CH_2), 42.13 (CH_2), 39.69 (CH), 30.11 (C), 25.33 (CH_2), 24.80 (CH_3), 24.50 (CH_3), 17.97 (CH_3), 11.83 (CH_3)

5.9.3 Synthesis of (*R*)-Mosher ester 3.28



3.10 **3.28**

To a solution of the hydroxy ketone **3.10** (26 mg, 41 μmol, 1 eq.) in pyridine (82 μl) were added (*S*)-MTPA-Cl (30 μl, 160 μmol, 4 eq.) and DMAP (0.5 mg, 4.1 μmol, 0.1 eq.) at RT. The reaction was stirred at RT for 20h, after which the mixture was poured in water (10 ml). The mixture was extracted with CH_2Cl_2 (4 x 10

ml), dried over $MgSO_4$ and concentrated. The product was purified by flash column chromatography (pentane/*Et2O* 1/1) and preparative HPLC, yielding **3.28** as a colorless oil (19 mg, 22 μmol, 54%).

Name: (3'*S*,7'*S*,10'*R*,8'*Z*)-2-(3-bromophenyl)-7'-((4"-methoxybenzyl)oxy)-10'-(((2"'-methoxyethoxy)methoxy)methyl)-2',8'-dimethyl-5'-oxododec-8'-en-3'-yl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate

Formula: $C_{43}H_{54}BrF_3O_9$

Molecular weight: 851.8 g/mol

R_f: 0.30 (pentane/Et_2O 1/1)

ESI-MS (m/z): 868.3 ($M+NH_4^+$)

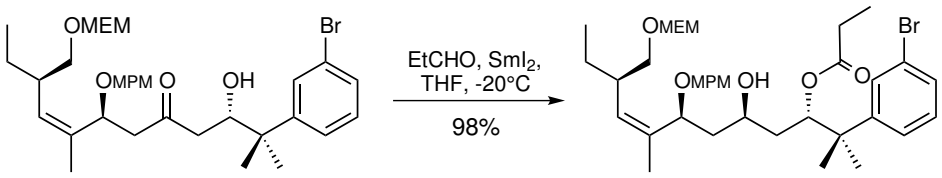
HR-MS: calculated for ($M+NH_4^+$) 868.3242, found 868.3236 (Δ 0.7 ppm)

^{1}H-NMR (500 MHz; CD_2Cl_2): δ (ppm) = 7.45 (app.t, J = 1.9 Hz, 1H), 7.44-7.35 (m, 5H), 7.34 (ddd, J = 7.9, 2.0, 1.0 Hz, 1H), 7.21 (ddd, J = 7.9, 1.9, 0.9 Hz, 1H), 7.20-7.17 (m, 1H), 7.13 (app. d, J = 8.4 Hz, 2H), 6.84 (app. d, J = 8.5 Hz, 2H), 5.82 (dd, J = 7.2, 3.9 Hz, 1H), 5.19 (app.d, J = 10.4, 1.5 Hz, 1H), 4.70 (dd, J = 10.3, 2.6 Hz, 1H), 4.645 (d, J = 6.6 Hz, 1H, A part of AB-spinsystem), 4.636 (d, J = 6.6 Hz, B part of AB-spinsystem), 4.30 (d, J = 10.8 Hz, 1H), 4.11 (d, J = 10.8 Hz, 1H), 3.79 (s, 3H), 3.64-3.61 (m, 2H), 3.52-3.48 (m, 2H), 3.46 (dd, J = 9.5, 5.8 Hz, 1H), 3.39-3.35 (m, 4H), 3.32 (s, 3H), 2.82 (dd, J = 15.4, 10.3 Hz, 1H), 2.62-2.53 (m, 3H), 2.11 (dd, J = 15.4, 2.7 Hz, 1H), 1.67 (d, J = 1.4 Hz, 3H), 1.54-1.45 (m, 1H), 1.22 (s, 3H), 1.16 (s, 3H), 1.18-1.09 (m, 1H), 0.76 (app. t, J = 7.4 Hz, 3H)

APT (125 MHz; CD_2Cl_2): δ (ppm) = 205.31 (C), 165.77 (C), 159.58 (C), 154.63 (CH), 147.98 (C), 135.21 (C), 132.60 (CH), 132.50 (C), 131.11 (C), 130.29 (CH), 130.20 (CH), 130.11 (CH), 129.95 (CH),129.80 (3? x CH), 128.68 (2 x CH), 127.91 (CH), 125.82 (CH), 123.82 (q, J(^{13}C-^{19}F) = 288.4 Hz, C), 122.92 (C), 113.99 (2 x CH), 95.84 (CH_2), 78.02 (CH), 73.56 (CH), 72.21 (CH_2),

71.68 (CH_2), 70.23 (CH_2), 67.12 (CH_2), 58.98 (CH_3), 55.62 (2 x CH_3), 47.71 (CH_2), 45.31 (CH_2), 42.30 (CH_2), 39.70 (CH), 30.11 (C), 25.35 (CH_3), 25.33 (CH_2), 23.99 (CH_3),17.96 (CH_3), 11.86 (CH_3) (One C not visible, in the region between 95-80 ppm)

5.9.4 Synthesis of hydroxy ester 3.25



3.10 **3.25**

To a solution of propionaldehyde (200μl, 2.79 mmol, 4 eq.) in THF (5 ml) was added SmI_2 (3.5 ml, 0.35 mmol, 0.5 eq., 0.1M solution in THF) at 0°C. The solution colored blue, changed rapidly to green and in the end to yellow. The solution was further cooled to -20°C and a solution of hydroxyketone **3.10** (443 mg, 0.70 mmol, 1 eq.) in THF (2 ml) was added using a double-ended needle and the flask containing the starting material was rinsed with THF (5 ml). The reaction was stirred at -20°C for 4 hours, after which TLC-analysis (hexane/acetone 8/2) showed complete conversion.[i] The reaction was quenched by adding $NaHCO_3$ (15 ml) and water (10 ml), extracted with EtOAc (3 x 25 ml), dried over $MgSO_4$ and concentrated. Purification using flash column chromatography (hexane/acetone 87.5/ 12.5) delivered alcohol **3.25** (478 mg, 98%).

Name: (3*S*,5*R*,7*S*,10*R*,8*Z*)-2-(3'-bromophenyl)-5-hydroxy-7-((4"-methoxybenzyl)-oxy)-10-(((2"'-methoxyethoxy)methoxy)methyl)-2,8-dimethyldodec-8-en-3-yl propionate

Formula: $C_{36}H_{53}BrO_8$

[i]There is only a very subtle difference in Rf -value, however, when looking at the back of the tlc-plate after staining with the molybdate containing reagent, the starting material has a red/pink glance, whereas the target material has a blue/green glance.

Molecular weight: 693.7 g/mol

R_f: 0.25 (hexane/acetone 8/2)

$[\alpha]_D$: -47.2° (c = 9.9 mg/ml in $CHCl_3$)

HR-MS: calculated for ($M+Na^+$) 715.2816, found 715.2797 (Δ 2.7 ppm)

^{1}H-NMR (500 MHz; CD_2Cl_2): δ (ppm) = 7.49 (app. t, J = 1.9 Hz, 1H), 7.33 (ddd, J = 7.8, 2.0, 1.0 Hz, 1H), 7.31 (ddd, J = 7.9, 2.0, 1.0 Hz, 1H), 7.20-7.14 (m, 3H), 6.84 (app. d, J = 8.7 Hz, 2H), 5.33 (dd, J = 10.8, 1.8 Hz, 1H), 5.18 (dd, J = 10.4, 1.6 Hz, 1H), 4.68 (d, J = 7.0 Hz, 1H, A part of AB-spinsystem), 4.67 (d, J = 7.0 Hz, 1H, B part of AB-spinsystem), 4.43 (dd, J = 9.1, 4.7 Hz, 1H), 4.36 (d, J = 11.2 Hz, 1H), 4.15 (d, J =11.2 Hz, 1H), 3.79 (s, 3H), 3.67-3.64 (m, 2H), 3.55-3.52 (m, 2H), 3.52-3.46 (m, 1H), 3.47 (dd, J = 9.5, 5.9 Hz, 1H), 3.39 (dd, J = 9.4, 6.8 Hz, 1H), 3.36 (s, 3H), 2.57-2.48 (m, 1H), 2.27 (qd, J = 7.6, 3.8 Hz, 2H), 1.87 (app. dt, J = 14.3, 9.0 Hz, 1H), 1.67 (d, J = 1.4 Hz, 3H), 1.51-1.31 (m, 4H), 1.300 (s, 3H), 1.297 (s, 3H), 1.19-1.12 (m, 1H), 1.08 (app. t, J = 7.6 Hz, 3H), 0.79 (app. t, J = 7.5 Hz, 3H)

APT (125 MHz; CD_2Cl_2): δ (ppm) = 174.87 (C), 159.24 (C), 148.91 (C), 135.48 (C), 132.15 (CH), 130.79 (C), 129.93 (CH), 129.86 (CH), 129.47 (CH), 129.37 (2 x CH), 125.41 (CH), 122.55 (C), 113.95 (2 x CH), 95.67 (CH_2), 76.84 (CH), 76.01 (CH), 71.93 (CH_2), 71.41 (CH_2), 69.61 (CH_2), 66.88 (CH_2), 59.17 (CH), 55.42 (CH_3), 41.90 (C), 40.80 (CH_2), 39.18 (CH), 38.12 (CH_2), 27.91 (CH_2), 25.26 (CH_3), 25.22 (CH_2), 24.21 (CH_3), 17.87 (CH_3), 11.81 (CH_3), 9.40 (CH_3)

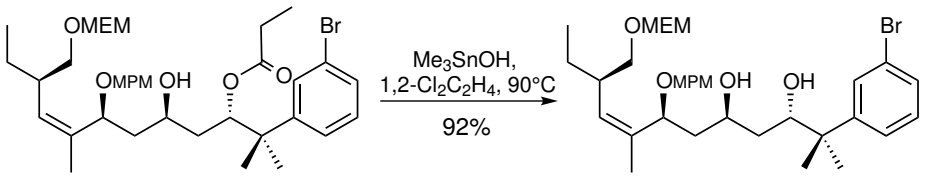
IR (HATR): 3504, 2961, 2929, 2877, 1735, 1718, 1612, 1513, 1462, 1366, 1301, 1246, 1176, 851, 822, 786, 700 cm^{-1}

Preparation of SmI_2(JOC 2012 3049)

Metallic samarium (601 mg, 4 mmol, 2 eq.) was first activated by stirring dry in a flask fitted with a rubber septum for 2 days under Ar atmosphere. After activation,

THF (16,5 ml) was added to the metal, followed by a red solution of I_2 (508 mg, 2 mmol, 1 eq.) in THF (3,5 ml). The septum was then replaced by a glass stopper and the brown reaction mixture was heated to 60°C. Stirring was continued for 24 h at 60°C, after which the solution turned dark blue. The mixture was cooled down to RT and the flask was fitted with a septum again and flushed with argon. This procedure yielded a solution of SmI_2 in THF with a concentration of approximately 0.1M. Upon stirring, the solution could be maintained for a couple of days. Two hours before using it, stirring was stopped.

5.9.5 Synthesis of diol 3.33



3.25 **3.33**

To a solution of **3.25** (52 mg, 74 μmol, 1 eq.) in 1,2-dichloroethane (0.74 ml)in a pressure tube was added Me_3SnOH (130 mg, 0.74 mmol, 10 eq.). The solution was stirred at 90°C for 9 days, after which the reaction mixture was poured in a mixture of a saturated aqueous solution of NH_4Cl (5 ml) and water (5 ml) and extracted with EtOAc (4 x 10 ml). After drying on $MgSO_4$ and concentrating, the product was purified using flash column chromatography (hexane/ EtOAC 6/4), yielding diol **3.33** (43 mg, 92%).

Name: (3*S*,5*S*,7*S*,10*R*,8*Z*)-2-(3'-bromophenyl)-7-((4"-methoxybenzyl)oxy)-10-(((2"'-methoxyethoxy)methoxy)methyl)-2,8-dimethyldodec-8-ene-3,5-diol

Formula: $C_{33}H_{49}BrO_7$

Molecular weight: 637.6 g/mol

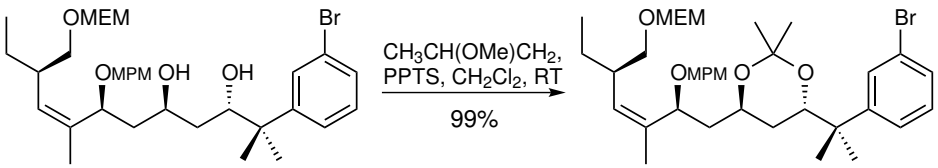
R_f: 0.31 (hexane/EtOAC 6/4)

HR-MS: calculated for ($M+OAc^-$) 695.2795, found 695.2804 (Δ 0.6 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.51 (app. t, J = 1.9 Hz, 1H), 7.33 (app. d, J = 1.8 Hz, 1H), 7.31 (app. d, J = 1.9 Hz, 1H), 7.23-7.19 (m, 2H), 7.16 (app. dd, J = 8.4, 7.4 Hz, 1H), 6.87-6.83 (m, 2H), 5.17 (app. dd, J= 10.5, 1.6 Hz, 1H), 4.68 (d, J = 6.7 Hz, 1H, A part of AB-spinsystem), 4.67 (d, J = 6.7 Hz, 1H, B part of AB-spinsystem), 4.51 (dd, J = 11.0, 2.8 Hz, 1H), 4.41 (d, J = 11.1 Hz, 1H), 4.18 (d, 11.0 Hz, 1H), 4.09-4.03 (m, 1H), 3.98 (dd, J = 10.5, 1.7 Hz, 1H), 3.79 (s, 3H), 3.67-3.64 (m, 2H), 3.55-3.52 (m, 2H), 3.48 (dd, J = 9.4, 5.8 Hz, 1H), 3.40-3.36 (m, 1H), 3.36 (s, 3H), 2.74 (bs, 1H), 2.54 -2.45 (m, 1H), 2.00 (ddd, J = 14.6, 10.7, 10.2 Hz, 1H), 1.73 (d, J = 1.5 Hz, 3H), 1.54-1.45 (m, 1H), 1.40 (ddd, J = 14.2, 10.5, 3.7 Hz, 1H), 1.35-1.27 (m, 2H), 1.30 (s, 3H), 1.29 (s, 3H), 1.20-1.10 (m, 1H), 0.78 (app. t, J = 7.5 Hz, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 159.43 (C), 150.15 (C), 135.57 (C), 131.94 (CH), 130.22 (C), 130.01 (CH), 129.75 (CH), 129.54 (2 x CH), 129.18 (CH), 125.53 (CH), 122.65 (C), 114.08 (2 x CH), 95.68 (CH_2), 78.40 (CH), 75.37 (CH), 71.92 (CH_2), 71.53 (CH_2), 70.19 (CH), 69.88 (CH_2), 66.90 (CH_2), 59.18 (CH_3), 55.42 (CH_3), 42.51 (C), 39.98 (CH_2), 39.44 (CH), 37.97 (CH_2), 25.15 (CH_2), 24.47 (CH_3), 23.77 (CH_3), 18.02 (CH_3), 11.88 (CH_3)

5.9.6 Synthesis of acetonide 3.34



3.33 **3.34**

To a solution of **3.33** (38 mg, 59 μmol, 1 eq.) in CH_2Cl_2 (4 ml) were added 2-methoxypropene (34 μlg, 0.35 mmol, 6 eq.) and pyridinium *p*-toluenesulfonic acid. The solution was stirred at RT for 1h20', after which TLC-analysis indicated complete consumption of the starting material. The reaction mixture was

quenched by adding a saturated aqueous solution of $NaHCO_3$ (5 ml) and extracted with CH_2Cl_2 (2 x 5 ml). After drying on $MgSO_4$ and concentrating, the product was purified using flash column chromatography (hexane/ EtOAC 8/2), yielding **3.33** (39 mg, 99%).

Name: (4*S*,6*R*)-4-(2'-(3"-bromophenyl)propan-2'-yl)-6-((2"'*S*,5"'*R*,3"'*Z*)-2"'-((4""-methoxybenzyl)oxy)-5"'-(((2""'-methoxyethoxy)methoxy)methyl)- 3"'-methylhept-3"'-en-1"'-yl)-2,2-dimethyl-1,3-dioxane

Formula: $C_{36}H_{53}BrO_7$

Molecular weight: 677.7 g/mol

R_f: 0.30 (hexane/EtOAC 8/2)

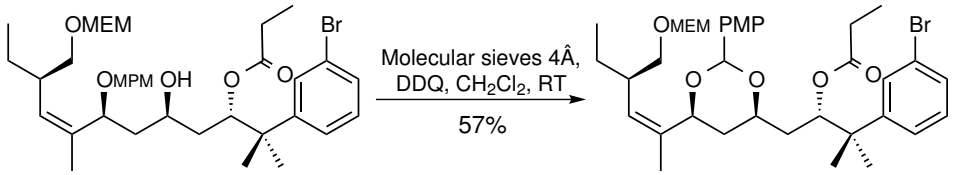
HR-MS: calculated for ($M+Na^+$) 699.2867, found 699.2865 (Δ 0.3 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.48 (app. t, J = 1.8 Hz, 1H), 7.30 (ddd, J = 7.9, 1.9, 1.0 Hz, 1H), 7.27 (ddd, J = 7.9, 1.7, 1.0 Hz, 1H), 7.23-7.19 (m, 2H), 7.13 (app. t, J = 7.9 Hz, 1H), 6.90-6.87 (m, 2H), 5.12 (app. dd, J = 10.4, 1.6 Hz, 1H), 4.70 (d, J = 6.7 Hz, 1H, A part of AB-spinsystem), 4.69 (d, J = 6.7 Hz, 1H, B part of AB-spinsystem), 4.36 (d, J = 11.3 Hz, 1H), 4.11 (dd, J = 10.1, 2.9 Hz, 1H), 4.06 (dd, J = 11.5 Hz, 1H), 3.83 (s, 3H), 3.82-3.76 (m, 1H), 3.74 (app. dd, J = 10.2, 6.0 Hz, 1H), 3.69-3.66 (m, 2H), 3.56-3.53 (m, 2H), 3.48 (dd, J = 9.4, 5.7 Hz, 1H), 3.39 (dd, J = 9.4, 7.0 Hz, 1H), 3.38 (s, 3H), 2.43-2.35 (m, 1H), 2.05 (ddd, J = 13.7, 10.2, 4.7 Hz, 1H), 1.67 (d, J = 1.4 Hz, 3H), 1.47-1.38 (m, 1H), 1.36-1.24 (m, 2H), 1.30 (s, 3H), 1.26 (s, 3H), 1.25 (s, 3H), 1.19 (s, 3H), 1.14-1.05 (m, 1H), 1.04 (ddd, J = 12.6, 9.4, 6.2 Hz, 1H), 0.66 (app. t, J = 7.5 Hz, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 159.25 (C), 149.62 (C), 136.40 (C), 131.26 (CH), 131.07 (C), 130.27 (CH), 129.81 (2 x CH), 129.43 (CH), 129.04 (CH), 125.60 (CH), 122.30 (C), 113.91 (2 x CH), 100.48 (C), 95.68 (CH_2), 73.27

(CH), 71.94 (CH_2), 71.92 (CH), 71.58 (CH_2), 69.36 (CH_2), 66.89 (CH_2), 64.65 (CH), 59.19 (CH_3), 55.41 (CH_3), 41.05 (C), 40.80 (CH_2), 39.33 (CH), 33.36 (CH_2), 25.20 (CH_2 + CH_3), 25.04 (CH_3), 24.40 (CH_3), 22.91 (CH_3), 18.04 (CH_3), 11.95 (CH_3)

5.9.7 Synthesis of MPM-acetal 3.35



3.25 **3.35**

A suspension of 4Å molecular sieves in a solution of **3.25** (51 mg, 72 μmol, 1 eq.) in CH_2Cl_2 was cooled to 0°C. Then, DDQ (6 ml, 108 μmol, 1.5 eq, 0.018 M in CH_2Cl_2) was added and the reaction mixture was stirred at RT for 3h, after which TLC-analysis (hexane/acetone 9/1) showed complete consumption of the starting material. The reaction mixture was filtered over a P4 filter and rinsed with CH_2Cl_2. After concentration, the product was purified by flash column chromatography (hexane/acetone 9/1, then hexane/Et_2O 6/4), providing **3.35** (28 mg, 57%).

Name: (2*S*)-3'-(3"-bromophenyl)-1-((4*R*,6*S*)-6-((4"'*R*,2"'*Z*)-4"'-(((2""-methoxyethoxy)methoxy)methyl)hex-2"'-en-2"'-yl)-2-(4""'-methoxyphenyl)-1,3-dioxan-4-yl)-3'-methyl- butan-2'-yl propionate

Formula: $C_{36}H_{51}BrO_8$

Molecular weight: 691.7 g/mol

R_f: 0.10 (hexane/acetone 9/1)

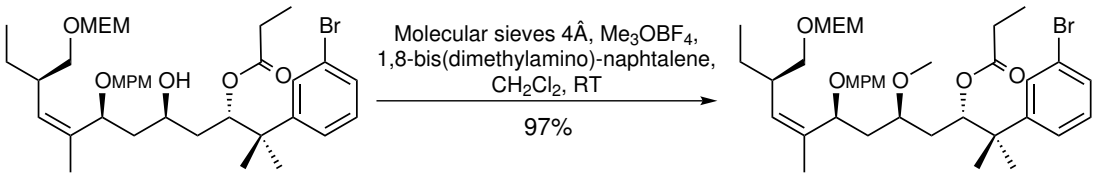
HR-MS: calculated for ($M+NH_4^+$) 708.3106, found 708.3092 (Δ 2.0 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.51 (app. t, J = 1.9 Hz, 1H), 7.45-7.41 (m, 2H), 7.34 (ddd, J = 5.2, 1.9, 1.0 Hz, 1H), 7.32 (ddd, J = 5.4, 1.9, 0.9 Hz,

1H), 7.16 (app. t, J = 7.9 Hz, 1H), 6.90-6.86 (m, 2H), 5.55 (dd, J = 10.3, 1.6 Hz, 1H), 5.34 (s, 1H), 5.01 (app. dd, J = 10.5, 1.5 Hz, 1H), 4.67 (s, 2H), 4.64 (dd, J = 11.4, 2.5 Hz, 1H), 3.80 (s, 3H), 3.70-3.63 (m, 3H), 3.52-3.49 (m, 2H), 3.42 (app. dd, J = 6.4, 1.1 Hz, 2H), 3.35 (s, 3H), 2.56-2.48 (m, 1H), 2.35 (app. qd, J = 7.6, 0.9 Hz, 2H), 1.76 (d, J = 1.5 Hz, 3H), 1.67-1.52 (m, 3H), 1.44 (ddd, J = 14.6, 10.4, 3.0 Hz, 1H), 1.31 (s, 3H), 1.29 (s, 3H), 1.26-1.17 (m, 2H), 1.14 (app. t, J = 7.6 Hz, 3H), 0.82 (app. t, J = 7.5 Hz, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 173.87 (C), 159.76 (C), 148.70 (C), 136.66 (C), 131.51 (C), 130.01 (CH), 129.86 (CH), 129.49 (CH), 129.23 (CH), 127.53 (2 x CH), 125.55 (CH), 122.55 (C), 113.52 (2 x CH), 100.24 (CH), 95.70 (CH2), 75.68 (CH), 75.53 (CH), 73.42 (CH), 71.91 (CH2), 71.38 (CH2), 66.87 (CH2), 59.12 (CH3), 55.41 (CH3), 42.11 (C), 39.57 (CH), 36.97 (CH2), 35.00 (CH2), 27.99 (CH2), 25.84 (CH3), 25.25 (CH2), 23.80 (CH3), 19.14 (CH3), 11.83 (CH3), 9.52 (CH3)

5.9.8 Synthesis of methyl ether 3.26



3.25 **3.26**

To a solution of alcohol **3.25** (811 mg, 1.17 mmol, 1 eq.) in CH_2Cl_2 (29 ml) were added molecular sieves (4Å) (470 mg), and the suspension was stirred at RT. After 30' 1,8-bis(dimethylamino)naphtalene (652 mg, 3.04 mmol, 2.6 eq.) and trimethyloxonium tetrafluoroborate (433 mg, 2.92 mmol, 2.5 eq.) were added, respectively. The mixture was stirred for 24h, after which TLC-analysis (hexane/acetone 8/2) showed complete conversion of the starting material. The reaction mixture was filtered, rinsed with 100 ml EtOAc and washed with a solution of $CuSO_4$ in water (2 x 80 ml, 1M). The aqueous phases were combined and extracted with EtOAc (3

x 150 ml). All organic phases were collected, dried over $MgSO_4$ and concentrated *in vacuo*. Flash column chromatography (hexane/EtOAc 7/3) delivered **3.26** (805 mg, 1.14 mmol, 97%) as a clear oil.

Name: (3*S*,5*R*,7*S*,10*R*,8*Z*)-2-(3'-bromophenyl)-5-methoxy-7-((4"-methoxybenzyl)-oxy)-10-(((2"'-methoxyethoxy)methoxy)methyl)-2,8-dimethyldodec-8-en-3-yl propionate

Formula: $C_{37}H_{55}BrO_8$

Molecular weight: 707.7 g/mol

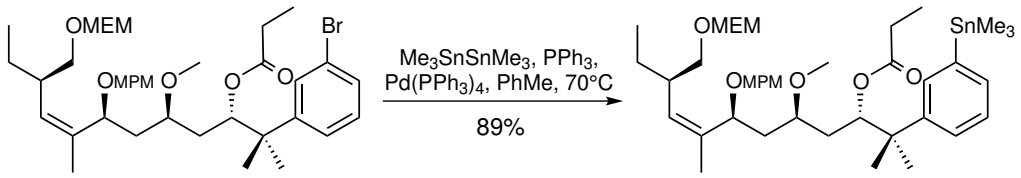
R_f: 0.31 (hexane/acetone 8/2)

HR-MS: calculated for ($M+NH_4^+$) 724.3419, found 724.3415 (Δ 0.5 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.50 (app. t, J = 1.9 Hz, 1H) 7.32 (app. dd, J = 7.9, 1.9 Hz, 2H) 7.18-7.13 (m, 3H) 6.85 (app. d, J = 8.7 Hz, 2H) 5.42 (dd, J = 9.8, 2.3 Hz, 1H) 5.12 (dd, J = 10.5, 1.0 Hz, 1H) 4.69 (d, J = 6.7 Hz, 1H, A part of AB-spinsystem) 4.68 (d, J = 6.7 Hz, 1H, B part of AB-spinsystem) 4.31 (d, J = 11.2 Hz, 1H) 4.19 (dd, J = 10.1, 2.6 Hz, 1H) 4.04 (d, J = 11.3 Hz, 1H) 3.81 (s, 3H) 6.68-3.65 (m, 2H) 3.56-3.53 (m, 2H) 3.47 (dd, J = 9.2, 5.9 Hz, 1H) 3.41-3.36 (m, 1H) 3.38 (s, 3H) 3.23 (s, 3H) 3.18-3.12 (m, 1H) 2.50-2.42 (m, 1H) 2.24 (app. q, J = 7.6 Hz, 2H) 2.04 (ddd, J = 14.1, 10.3, 3.7 Hz, 1H) 1.67 (d, J = 1.3 Hz, 3H) 1.53-1.38 (m, 3H) 1.33-1.27 (m, 1H) 1.275 (s, 3H) 1.266 (s, 3H) 1.18-1.10 (m, 1H) 1.06 (app. t, J= 7.6 Hz, 3H) 0.77 (app. t, J = 7.4 Hz, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 173.88 (C), 159.11 (C), 149.03 (C), 136.46 (C), 131.20 (C), 130.00 (CH), 129.76 (CH), 129.36 (CH), 129.22 (2 x CH), 125.55 (CH), 122.45 (C), 113.86 (2 x CH), 95.66 (CH_2), 76.36 (CH),74.93 (CH), 73.23 (CH), 71.93 (CH_2), 71.54 (CH_2), 69.69 (CH_2), 66.88 (CH_2), 59.18 (CH_3), 56.58 (CH_3), 55.44 (CH_3), 42.04 (C), 39.33 (CH), 37.49 (CH_2), 35.20 (CH_2), 27.90 (CH_2), 25.56 (CH_3), 25.22 (CH_2), 24.04 (CH_3), 18.04 (CH_3), 11.95 (CH_3), 9.50 (CH_3)

5.9.9 Synthesis of stannane 3.9



3.26 **3.9**

In a pressure tube, **3.26** (805 mg, 1.14 mmol, 1 eq.) was dissolved in toluene (11 ml), and hexamethylditin (745 mg, 2.27 mmol, 2 eq.) and PPh_3 (119 mg, 0.46 mmol, 0.4 eq.) are added. After the addition of tetrakis(triphenylphosphine)palladium (60 mg, 0.052 mmol, 4.6 mol%), the solution turned yellow, and it was heated to 70°C, upon which the color disappeared. The reaction was followed using TLC-analysis (hexane/acetone 9/1). After 20h of refluxing, the formation of Pd black is clearly visible, and thus a fresh portion of catalyst was added (40 mg, 0.035 mmol, 3.0 mol%). Stirring was continued at 70°C, and after 44h (in total), a third portion of catalyst (30 mg, 0.027 mmol, 2.4 mol%, 10 mol% in total) was added, after which the reaction mixture was stirred for another 22h (65h in total) at 70°C. The reaction mixture was then poured into a mixture of a saturated aqueous $NaHCO_3$ solution (15 ml) and water (15 ml) and diluted with EtOAc (30 ml). The phases were separated and the aqueous solution was extracted with EtOAc (2 x 30 ml). The organic phases were combined, dried over $MgSO_4$ and concentrated. Flash column chromatography (pentane/Et_2O 6/4) yielded stannane **3.9** (801 mg, 1.01 mmol, 89%).

Name: (3'*S*,5'*R*,7'*S*,10'*R*,8'*Z*)-5'-methoxy-7'-((4"-methoxybenzyl)oxy)-10'-(((2"'-methoxyethoxy)methoxy)methyl)-2',8'-dimethyl-2'-(3""-(trimethylstannyl)-phenyl)dodec-8'-en-3'-yl propionate

Formula: $C_{40}H_{64}O_8Sn$

Molecular weight: 791.7 g/mol

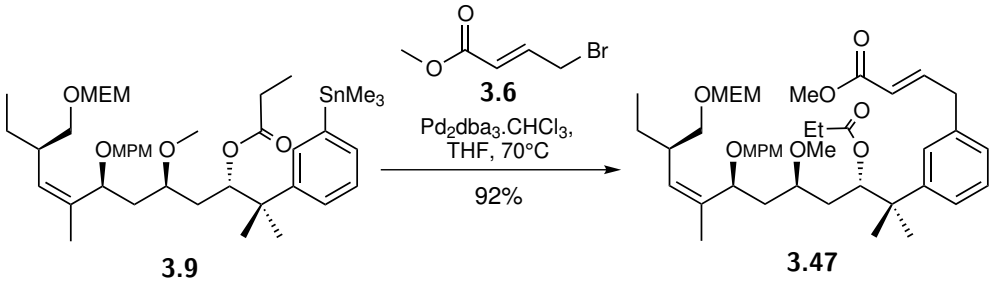
R_f: 0.29 (pentane/Et_2O 6/4)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.48 (app. d, J = 2.2 Hz, 1H), 7.35-7.23 (m, 3H), 7.16 (app. d, J = 8.7 Hz, 2H), 6.84 (app. d, J = 8.7 Hz, 2H), 5.51 (dd, J = 9.8, 2.1 Hz, 1H), 5.12 (dd, J = 10.3, 1.4 Hz, 1H), 4.69 (d, J = 6.7 Hz, 1H, A part of AB-spinsystem), 4.68 (d, J = 6.7 Hz, 1H, B part of AB-spinsystem), 4.31 (d, J = 11.1 Hz, 1H), 4.20 (dd, J = 9.9, 2.9 Hz, 1H), 4.04 (d, J = 11.2 Hz, 1H), 3.80 (s, 3H), 3.68-3.65 (m, 2H), 3.56-3.53 (m, 2H), 3.46 (dd, J = 9.5, 5.7 Hz, 1H), 3.39 (dd, J = 9.6, 6.7 Hz, 1H), 3.37 (s, 3H), 3.22 (s, 3H), 3.18-3.13 (m, 1H), 2.51-2.42 (m, 1H), 2.22 (app. q, J = 7.6 Hz, 2H), 2.03 (ddd, J = 14.1, 10.0, 4.0 Hz, 1H), 1.66 (d, J = 1.4 Hz, 3H), 1.52-1.40 (m, 3H), 1.32-1.26 (m, 1H), 1.31 (s, 3H), 1.29 (s, 3H), 1.19-1.09 (m, 1H), 1.04 (app. t, J = 7.6 Hz, 3H), 0.76 (app. t, J = 7.5 Hz, 3H), 0.27 (s, 9H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 174.00 (C), 159.12 (C), 145.86 (C), 141.76 (C), 136.44 (C), 133.84 (CH), 133.71 (CH), 131.23 (C), 131.12 (CH), 129.19 (2 x CH), 127.81 (CH), 126.72 (CH), 113.84 (2 x CH), 95.66 (CH_2), 76.79 (CH), 75.05 (CH), 73.36 (CH), 71.93 (CH_2), 71.51 (CH_2), 69.70 (CH_2), 66.87 (CH_2), 59.18 (CH_3), 56.46 (CH_3), 55.42 (CH_3), 41.95 (C), 39.26 (CH), 37.67 (CH_2), 35.18 (CH_2), 27.93 (CH_2), 26.03 (CH_3), 25.21 (CH_2), 23.66 (CH_3), 18.04 (CH_3), 11.91 (CH_3), 9.52 (CH_3), -9.41 (3 x CH_3)

5.10 Completion of the synthesis of pelofen

5.10.1 Synthesis of ester 3.47



In a pressure tube were added respectively methyl-E-4-bromo-2-butenoate (**3.6**) (229 μl, 1.91 mmol, 2 eq.) and $Pd_2(dba)_3 \cdot CHCl_3$ (15 mg, 14 mol, 1.5 mol%) to a solution of stannane **3.9** (757 mg, 0.96 mmol, 1 eq.) in THF (4.8 ml). The red reaction mixture turned brightly yellow upon heating to 70°C. After 3h of stirring at 70°C, TLC-analysis (pentane/Et_2O 1/1) showed complete conversion of the starting material, upon which the mixture was poured into a saturated aqueous solution of $NaHCO_3$ (30 ml), diluted with CH_2Cl_2 (30 ml) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (2 x 30 ml), the organic phases were combined, dried over $MgSO_4$, and concentrated. Flash column chromatography purification delivered the *trans*-ester **3.47** (639 mg, 0.88 mmol, 92%), together with a minor amount of the *cis*-ester.

Name: methyl (*E*)-4-(3'-((3" *S*,5" *R*,7" *S*,10" *R*,8" *Z*)-5"-methoxy-7"-((4"'-methoxybenzyl)oxy)-10"-(((2""-methoxyethoxy)methoxy)methyl)-2",8"-dimethyl-3"-(propionyloxy)dodec-8"-en-2"-yl)phenyl)but-2-enoate

Formula: $C_{42}H_{62}O_{10}$

Molecular weight: 726.9 g/mol

R_f: 0.31 (pentane/Et_2O 4/6)

ESI-MS (m/z): 744.3 ($M+NH_4^+$)

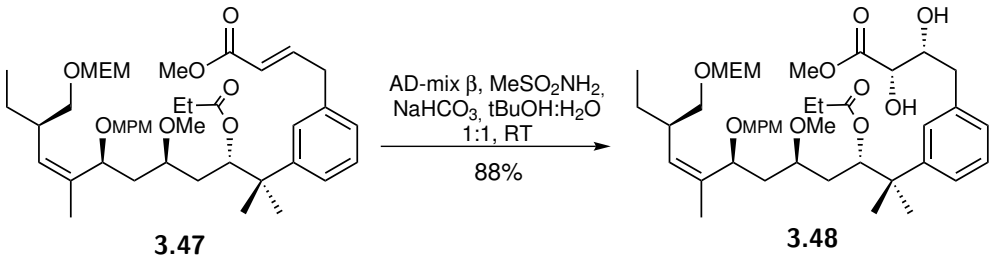
HR-MS: calculated for ($M+NH_4^+$) 744.4681, found 744.4674 (Δ 1.0 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.26-7.15 (m, 5H), 7.08 (app. dt, J = 15.6, 6.8 Hz, 1H), 6.98 (app. dt, J = 6.9, 1.7 Hz, 1H), 6.85 (app. d, J = 8.7 Hz, 2H), 5.80 (app. dt, J = 15.6, 1.6 Hz, 1H), 5.47 (dd, J = 10.1, 1.9 Hz, 1H), 5.12 (dd, J = 10.4, 1.5 Hz, 1H), 4.68(d, J = 6.7 Hz, 1H, A part of AB-spinsystem), 4.67 (d, J = 6.7 Hz, 1H, B part of AB-spinsystem), 4.32 (d, J = 11.3 Hz, 1H), 4.20 (dd, J = 10.0, 3.0 Hz, 1H), 4.05 (d, J = 11.3 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.68-3.65 (m, 2H), 3.56-3.53 (m, 2H), 3.48 (app. dd, J = 6.7, 1.8 Hz, 2H), 3.46 (dd, J = 9.2, 5.9 Hz, 1H), 3.39 (dd, J =

9.4, 6.7 Hz, 1H), 3.37 (s, 3H), 3.21 (s, 3H), 3.18-3.12 (m, 1H), 2.51-2.42 (m, 1H), 2.21 (app. q, J = 7.6 Hz, 2H), 2.03 (ddd, J = 14.2, 10.2, 3.9 Hz, 1H), 1.67 (d, J = 1.4 Hz, 3H), 1.52-1.38 (m, 3H), 1.33-1.26 (m, 1H), 1.29 (s, 3H), 1.27 (s, 3H), 1.19-1.09 (m, 1H), 1.04 (app. t, J = 7.6 Hz, 3H), 0.77 (app. t, J = 7.4 Hz, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 173.94 (C), 167.13 (C), 159.12 (C), 147.92 (CH), 147.07 (C), 137.33 (C), 136.46 (C), 131.23 (C), 131.11 (CH), 129.15 (2 x CH), 128.50 (CH), 127.20 (CH), 126.63 (CH), 125.14 (CH), 121.95 (CH), 113.84 (2 x CH), 95.66 (CH_2), 76.65 (CH), 74.97 (CH), 73.29 (CH), 71.93 (CH_2), 71.50 (CH_2), 69.65 (CH_2), 66.88 (CH_2), 59.18 (CH_3), 56.44 (CH_3), 55.42 (CH_3), 51.57 (CH_3), 41.87 (C), 39.28 (CH), 38.87 (CH_2), 37.61 (CH_2), 35.12 (CH_2), 27.91 (CH_2), 25.74 (CH_3), 25.22 (CH_2), 23.84 (CH_3), 18.03 (CH_3), 11.90 (CH_3), 9.49 (CH_3)

5.10.2 Synthesis of diol 3.48



3.47 **3.48**

To a solution of unsaturated ester **3.47** (500 mg, 0.69 mmol, 1 eq.) in t-BuOH (6.8 ml) and water (6.8 ml) were added $NaHCO_3$ (555 mg, 6.61 mmol, 9.6 eq.), methanesulfonamide (131 mg, 1.38 mmol, 2 eq.) and AD-mix β (2.48 g), and the orange-brown biphasic mixture was stirred vigorously. As the reaction proceeded, the color of the mixture changed to yellow-brown. After 45h, TLC-analysis (pentane/ Et_2O 4/6) indicated full conversion of the starting material, and the reaction was quenched by addition of a saturated aqueous solution of $Na_2S_2O_3$ (24 ml). After stirring for 2h at RT, the color of the aqueous phase had switched from dark brown to clear yellow to beige brown. The reaction mixture was

transferred to a separation funnel containing water (50 ml) using $CHCl_3$ (70 ml). After extraction, the phases were separated and the aqueous phase was further extracted with $CHCl_3$ (4 x 70 ml). The combined organic phases were dried over $MgSO_4$ and concentrated. Flash column chromatography (hexane/ EtOAc 4/6) provided diol **3.48** (460 mg, 0.60 mmol, 88%) as a clear oil.

Name: methyl (2*S*,3*R*)-2,3-dihydroxy-4-(3'-((3" *S*,5" *R*,7" *S*,10" *R*,8" *Z*)-5"-methoxy-7"-((4"'-methoxybenzyl)oxy)-10"-(((2""-methoxyethoxy)methoxy)methyl)-2",8"-dimethyl-3"-(propionyloxy)dodec-8"-en-2"-yl)phenyl)butanoate

Formula: $C_{42}H_{64}O_{12}$

Molecular weight: 761.0 g/mol

R_f: 0.16 (hexane/EtOAc 1/1)

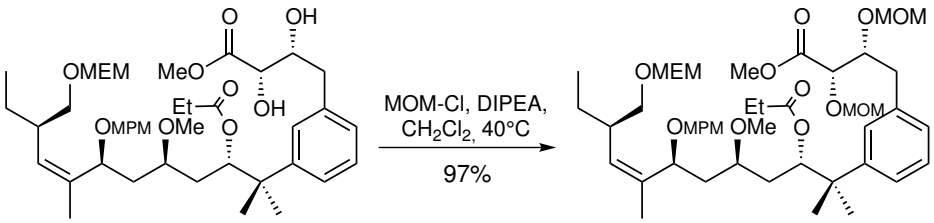
ESI-MS (m/z): 778.3 ($M+NH_4^+$)

HR-MS: calculated for ($M+NH_4^+$) 778.4736, found 778.4731 (Δ 0.7 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.32 (app. t, J = 1.8 Hz, 1H), 7.24-7.15 (m, 4H), 7.06 (app. dt, J = 6.9, 1.7 Hz, 1H), 6.85 (app. d, J = 8.7 Hz, 2H), 5.4 (dd, J = 10.6, 1.3 Hz, 1H), 5.11 (app. dd, J = 10.4, 1.5 Hz, 1H), 4.69 (d, J = 6.7 Hz, 1H, A part of AB-spinsystem), 4.68 (d, J = 6.7 Hz, 1H, B part of AB-spinsystem), 4.31 (d, J = 11.2 Hz, 1H), 4.18 (app. dd, J = 10.2, 2.6 Hz, 1H), 4.15 (app. ddd, J = 8.2, 6.0, 2.0 Hz, 1H), 4.05 (app. bs, 1H), 4.03 (d, J = 11.2 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.69-3.65 (m, 2H), 3.56-3.53 (m, 2H), 3.46 (dd, J = 9.5, 6.3 Hz, 1H), 3.38 (dd, J = 9.4, 6.6 Hz, 1H), 3.37 (s, 3H), 3.24 (s, 3H), 3.15 (dddd, J = 10.3, 8.2, 3.4, 2.1 Hz, 1H), 2.96 (dd, J = 13.6, 8.5 Hz, 1H), 2.89 (dd, J = 13.6, 5.9 Hz, 1H), 2.69 (bs, 1H), 2.51-2.42 (m, 1H), 2.17 (app. dq, J = 7.5, 0.7 Hz, 2H), 2.03 (ddd, J = 14.1, 10.4, 3.6 Hz, 1H), 1.66 (d, J = 1.4 Hz, 3H), 1.60-1.45 (m, 3H), 1.38 (ddd, J = 14.7, 10.4, 1.3 Hz, 1H), 1.30 (s, 3H), 1.27 (s, 3H), 1.13 (ddd, J = 13.5, 8.6, 7.5 Hz, 1H), 1.00 (app. t, J = 7.6 Hz, 3H), 0.76 (app. t, J = 7.5 Hz, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 174.20 (C), 173.89 (C), 159.14 (C), 147.07 (C), 137.57 (C), 133.45 (C), 131.13 (C), 131.09 (CH), 129.21 (2 x CH), 128.44 (CH), 127.99 (CH), 127.34 (CH), 124.58 (CH), 113.85 (2 x CH), 95.65 (CH_2), 76.73 (CH), 75.31 (CH), 73.32 (CH), 73.09 (CH), 72.66 (CH), 71.93 (CH_2), 71.49 (CH_2), 69.62 (CH_2), 66.89 (CH_2), 59.18 (CH_3), 56.82 (CH_3), 55.43 (CH_3), 52.69 (CH_3), 41.81 (C), 40.42 (CH_2), 39.27 (CH), 37.57 (CH_2), 35.05 (CH_2), 27.83 (CH_2), 25.48 (CH_3), 25.19 (CH_2), 23.42 (CH_3), 18.01 (CH_3), 11.92 (CH_3), 9.45 (CH_3)

5.10.3 Synthesis of bis-MOM-ether 3.8



3.48 **3.8**

In a pressure tube, fitted with a rubber septum, were added diisopropylethylamine (91 μl, 0.52 mmol, 5.5 eq.) and methoxymethylchloride (210 μl, 0.47 mmol, 5.0 eq., 2.25 M solution in MeOAc), respectively, to a solution of diol **3.48** (72 mg, 0.095 mmol, 1 eq.) in CH_2Cl_2 (473 μl) at 0°C. The pressure tube was sealed with a cap and the reaction mixture was refluxed for 27h, after which TLC-analysis (hexane/acetone 8/2) indicated complete conversion of the starting material. The reaction was quenched by pouring the mixture in a separation funnel containing water (40 ml), and diluted with CH_2Cl_2 (40 ml). The aqueous phase was further extracted with CH_2Cl_2 (3 x 40 ml). The organic phases were combined, dried over $MgSO_4$, and concentrated. After flash column chromatography (hexane/acetone 8/2), ester **3.8** was obtained (78 mg, 0.091 mmol, 97%) as a yellow oil.

Name: Methyl (2*S*,3*R*)-4-(3'-((3" *S*,5" *R*,7" *S*,10" *R*,8" *Z*)-5"-methoxy-7"-((4"'-methoxybenzyl)oxy)-10"-(((2""-methoxyethoxy)methoxy)methyl)-2",8"-di-me-

thyl-3”-(propionyloxy)dodec-8”-en-2”-yl)phenyl)-2,3-bis(methoxymethoxy) butanoate

Formula: $C_{46}H_{72}O_{14}$

Molecular weight: 849.1 g/mol

R_f: 0.36 (hexane/acetone 7/3)

ESI-MS (m/z): 866.4 ($M+NH_4^+$)

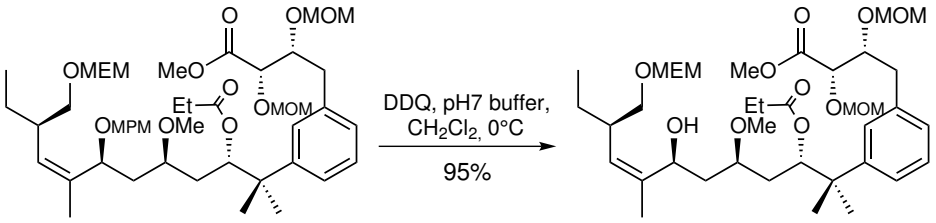
HR-MS: calculated for ($M+NH_4^+$) 866.5260, found 866.5255 (Δ 0.6 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.26-7.16 (m, 5H), 7.08 (app. dt, J = 6.6, 1.9 Hz, 1H), 6.85 (app. d, J = 8.7 Hz, 2H), 5.49 (dd, J = 10.5, 1.4 Hz, 1H), 5.12 (dd, J = 10.4, 1.4 Hz, 1H), 4.77 (d, J = 7.0 Hz, 1H, A part of AB-spinsystem 1), 4.72 (d, J = 7.0 Hz, 1H, B part of AB-spinsystem 1), 4.69 (d, J = 6.7 Hz, 1H, A part of AB-spinsystem 2), 4.67 (d, J = 6.7 Hz, 1H, B part of AB-spinsystem 2), 4.48 (d, J = 7.1 Hz, 1H), 4.39 (d, J = 7.1 Hz, 1H), 4.32 (d, J = 11.3 Hz, 1H), 4.22-4.15 (m, 3H), 4.05 (d, J = 11.3 Hz, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.68-3.65 (m, 2H), 3.56-3.52 (m, 2H), 3.49-3.45 (m, 1H), 3.47 (s, 3H), 3.41-3.35 (m, 1H), 3.37 (s, 3H), 3.21 (s, 3H), 3.16-3.11 (m, 1H), 3.16 (s, 3H), 2.97 (dd, J = 13.8, 7.6 Hz, 1H), 2.93 (dd, J = 13.8, 6.3 Hz, 1H), 2.51-2.43 (m, 1H), 2.22 (app. q, J = 7.6 Hz, 2H), 2.02 (ddd, J = 14.1, 10.1, 3.9 Hz, 1H), 1.66 (d, J = 1.4 Hz, 3H), 1.52-1.45 (m, 2H), 1.39 (ddd, J = 14.7, 10.1, 1.5 Hz, 1H), 1.31-1.24 (m, 1H), 1.28 (s, 3H), 1.26 (s, 3H), 1.18-1.10 (m, 1H), 1.05 (app. t, J = 7.6 Hz, 3H), 0.77 (app. t, J = 7.4 Hz, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 173.93 (C), 171.25 (C), 159.12 (C), 146.93 (C), 137.57 (C), 136.43 (C), 131.23 (C), 131.12 (CH), 129.15(2 x CH), 128.29 (CH), 127.87 (CH), 127.37 (CH), 124.92 (CH), 113.84 (2 x CH), 97.22 (CH_2), 96.85 (CH_2), 95.66 (CH_2), 79.74 (CH), 77.26 (CH), 76.66 (CH), 74.96 (CH), 73.28 (CH), 71.93 (CH_2), 71.49 (CH_2), 69.63 (CH_2), 66.88 (CH_2), 59.18 (CH_3), 56.67 (CH_3), 56.40 (CH_3), 55.94 (CH_3), 55.42 (CH_3), 52.05 (CH_3),

41.86 (C), 39.27 (CH), 38.05 (CH_2), 37.63 (CH_2), 35.18 (CH_2), 27.90 (CH_2), 25.95 (CH_3), 25.21 (CH_2), 23.55 (CH_3), 18.04 (CH_3), 11.89 (CH_3), 9.51 (CH_3)

5.10.4 Synthesis of alcohol 3.49



3.8 **3.49**

To a solution of **3.8** (71 mg, 0.084 μmol, 1 eq.) in CH_2Cl_2 (4.2 ml) and pH 7 phosphate buffer (0.42 ml) at 0°C was added 2,3-dichloro-5,6-dicyanobenzoquinone (190 mg, 836 mmol, 10 eq.) in one portion. The reaction mixture was stirred at 0°C for 1h, after which TLC-analysis (hexane/acetone 6/4) showed complete conversion of the starting material. The reaction was quenched using a saturated aqueous solution of $NaHCO_3$ (4.4 ml) and water (5 ml), transferred to a separation funnel with CH_2Cl_2 (6 ml) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 ml), the combined organic phases were dried over $MgSO_4$ and concentrated. Gradual flash column chromatography (hexane/EtOAc 4/6 to hexane/ acetone 8/2) provided alcohol **3.49** as a colorless oil (58 mg, 0.080 μmol, 95%).

Name: methyl (2*S*,3*R*)-4-(3'-((3"*S*,5"*R*,7"*S*,10"*R*,8"*Z*)-7"-hydroxy-5"-methoxy-10"-(((2"'-methoxyethoxy)methoxy)methyl)-2",8"-dimethyl-3"-(propionyloxy)dodec-8"-en-2"-yl)phenyl)-2,3-bis(methoxymethoxy)butanoate

Formula: $C_{38}H_{64}O_{13}$

Molecular weight: 728.9 g/mol

R_f: 0.1 (hexane/acetone 8/2)

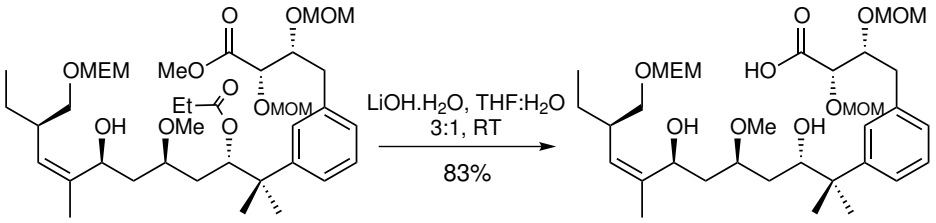
ESI-MS (m/z): 746.4 ($M+NH_4^+$)

HR-MS: calculated for (M+OAc^-) 787.4480, found 787.4454 (Δ 4.3 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.28-7.21 (m, 3H), 7.10 (app. dt, J = 6.9, 1.7 Hz, 1H), 5.46 (dd, J = 8.8, 3.0 Hz, 1H), 4.94 (dd, J = 10.2, 1.5 Hz, 1H), 4.77 (d, J = 7.0 Hz, 1H, A part of AB-spinsystem 1), 4.72 (d, J = 7.0 Hz, 1H, B part of AB-spinsystem 1), 4.68 (d, J = 7.0 Hz, 1H, A part of AB-spinsystem 2), 4.66 (d, J = 7.0 Hz, 1H, B part of AB-spinsystem 2), 4.49 (d, J = 7.2 Hz, 1H), 4.48 (dd, J = 8.6, 5.0 Hz, 1H), 4.38 (d, J = 7.2 Hz, 1H), 4.20 (ddd, J = 7.6, 6.4, 2.9 Hz, 1H), 4.17 (d, J = 2.9 Hz, 1H), 3.75 (s, 3H), 3.65-3.62 (m, 2H), 3.55-3.52 (m, 2H), 3.51-3.47 (m, 1H), 3.47 (s, 3H), 3.38 (s, 3H), 3.26 (app. t, J = 8.9 Hz, 1H), 3.21 (s, 3H), 3.16 (s, 3H), 3.14-3.07 (m, 1H), 2.99 (dd, J = 13.7, 7.6 Hz, 1H, part of AB2 system?), 2.94 (dd, J = 13.8, 6.2 Hz, 1H, part of AB2 system?), 2.80 (bs, 1H), 2.60-2.51 (m, 1H), 2.30 (app. q, J = 7.7 Hz, 2H), 1.84 (ddd, J = 14.2, 8.5, 6.4 Hz, 1H), 1.66 (d, J = 1.4 Hz, 3H), 1.49-1.39 (m, 2H), 1.37-1.30 (m, 1H), 1.32 (s, 3H), 1.28 (s, 3H), 1.20-1.14 (m, 1H), 1.12 (app. t, J = 7.6 Hz, 3H), 0.82 (app. T, J = 7.3 Hz, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 174.02 (C), 171.23 (C), 146.70 (C), 139.60 (C), 137.68 (C), 130.37 (CH), 128.40 (CH), 127.85 (CH), 127.48 (CH), 125.01 (CH), 97.19 (CH_2), 96.84 (CH_2), 95.53 (CH_2), 79.70 (CH), 77.26 (CH), 76.83 (CH), 76.65 (CH), 71.90 (CH_2), 71.28 (CH_2), 67.00 (CH_2), 66.22 (CH), 59.15 (CH_3), 56.79 (CH_3), 56.68 (CH_3), 55.95 (CH_3), 52.09 (CH_3), 42.07 (C), 39.27 (CH), 38.46 (CH_2), 38.08 (CH_2), 35.50 (CH_2), 28.03 (CH_2), 26.37 (CH_3), 25.05 (CH_2), 23.09 (CH_3), 18.25 (CH_3), 11.91 (CH_3), 9.52 (CH_3)

5.10.5 Synthesis of carboxylic acid 3.50



3.49 **3.50**

To a solution of **3.49** (20 mg, 27 μmol, 1 eq.) in a mixture of THF (0.5 ml) and water (0.5 ml) was added $LiOH \cdot H_2O$ (12 mg, 0.27 mmol, 10 eq.) at RT. TLC-analysis (CH_2Cl_2/ MeOH/AcOH 95/5/0.5) indicated hydrolysis of the methyl ester after 16h, but the reaction was stirred further for 7 days in order to complete the hydrolysis of the propionate ester. After 7 days, the reaction mixture was poured into a saturated aqueous solution of NH_4Cl (10 ml), and acidified with HCl (2ml, 0.1 M) until the pH reached 5-6. The reaction mixture was transferred to a separation flask using CH_2Cl_2 (10 ml) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (4 x 10 ml), the organic phases were combined, dried over $MgSO_4$, and concentrated. The *seco*-acid was purified using flash column chromatography (CH_2Cl_2/ MeOH/ AcOH 96/4/0.5), the fractions containing target material were combined, washed with water (3 x 25 ml), dried over $MgSO_4$, and concentrated, delivering **3.50** (15 mg, 23 μmol, 83%) as an amorphous solid.

Name: (2*S*,3*R*)-4-(3'-((3"*S*,5"*R*,7"*S*,10"*R*,8"*Z*)-3",7"-dihydroxy-5"-methoxy-10"-(((2"'-methoxyethoxy)methoxy)methyl)-2",8"-dimethyl-dodec-8"-en-2"-yl)-phenyl)-2,3-bis(methoxymethoxy)butanoic acid

Formula: $C_{34}H_{58}O_{12}$

Molecular weight: 658.8 g/mol

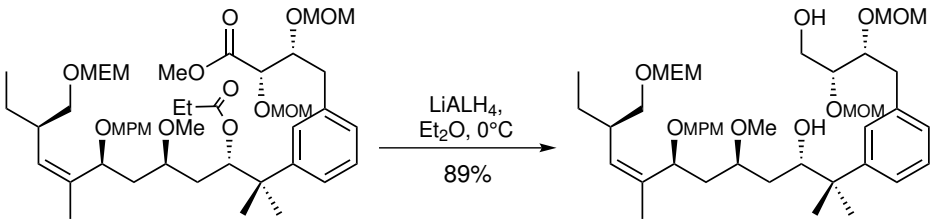
R_f: 0.1 (CH_2Cl_2/ MeOH/AcOH 95/5/0.5)

ESI-MS (m/z): 657.3 ($M\text{-}H^+$)

^{1}H-NMR (500 MHz; C_6D_6): δ (ppm) = 7.26 (app. s, 1H), 7.23-7.19 (m, 1H), 7.16-7.13 (m, 2H), 4.88 (dd, J = 10.1, 1.4 Hz, 1H), 4.77 (dd, J = 9.4, 3.6 Hz, 1H), 4.75 (d, J = 6.8 Hz, 1H), 4.63 (d, J = 6.9 Hz, 1H), 4.61 (d, J = 6.8 Hz, 1H), 4.56 (d, J = 6.6 Hz, 1H, A part of AB-spinsystem), 4.53 (d, J = 6.6 Hz, 1H, B part of AB-spinsystem), 4.52 (d, J = 6.9 Hz, 1H), 4.41 (app. td, J = 6.6, 4.1 Hz, 1H), 4.29 (d, J = 4.1 Hz, 1H), 4.01 (dd, J = 10.0, 2.2 Hz, 1H), 3.61-3.50 (m, 3H), 3.38 (dd, J = 9.3, 5.0 Hz, 1H), 3.33-3.29 (m, 2H), 3.25 (s, 3H), 3.25-3.21 (m, 1H), 3.18-3.06 (m, 2H), 3.13 (2 x s, 6H), 3.11(s, 3H), 2.65-2.56 (m, 1H), 2.24 (ddd, J = 14.4, 9.4, 5.1 Hz, 1H), 1.79 (d, J = 1.4 Hz, 3H), 1.70-1.59 (m, 3H), 1.46 (s, 3H), 1.39 (s, 3H), 1.39-1.30 (m, 1H), 1.12-1.03 (m, 1H), 0.82 (app. t, J = 7.4 Hz, 3H)

APT (125 MHz; C_6D_6): δ (ppm) = 172.69 (C), 147.83 (C), 140.41 (C), 138.21 (C), 129.68 (CH), 128.88 (CH), 128.50 (CH), 127.59 (CH), 125.01 (CH), 97.26 (CH_2), 96.54 (CH_2), 95.34 (CH_2), 80.07 (CH), 78.71 (CH), 78.08 (CH), 76.55 (CH), 72.10 (CH_2), 71.58 (CH_2), 67.24 (CH_2), 65.96 (CH), 58.61 (CH_3), 56.36 (CH_3), 56.16 (CH_3), 55.57 (CH_3), 42.83 (C), 39.26 (CH), 38.32 (CH_2), 37.60 (CH_2), 35.37 (CH_2), 26.21 (CH_3), 25.39 (CH_2), 23.64 (CH_3), 18.33 (CH_3), 12.01 (CH_3)

5.10.6 Synthesis of primary alcohol 3.53



3.8 **3.53**

To a flask, containing a suspension of $LiAlH_4$ (24 mg, 0.64 mmol, 3 eq.) in dithylether (5 ml) was added at 0°C a solution of **3.8** (180 mg, 0.21 mmol, 1 eq.) in dithylether (5 ml) via a double-ended needle. The reaction was stirred at RT, and extra $LiAlH_4$ was added until TLC-analysis (hexane/acetone 7/3) indicated

complete conversion of the starting material. The excess $LiAlH_4$ was destroyed by adding EtOAc (5 ml) at 0°C, after which a saturated aqueous solution of Rochelle's salt (10 ml) was added and the suspension was stirred for 45' at RT. The phases were separated, and the aqueous phase was extracted with EtOAc (5 x 10 ml), the organic phases were combined, dried over $MgSO_4$, and concentrated. Flash column chromatography (hexane/EtOAc 2/8) delivered diol **3.53** (144 mg, 0.19 mmol, 89%) as a clear oil.

Name: (3*S*,5*S*,7*S*,10*R*,8*Z*)-2'-(3"-((2'*R*,3'*R*)-4'-hydroxy-2',3'-bis(methoxymethoxy) butyl)phenyl)-5-methoxy-7-((4"'-methoxybenzyl)oxy)-10-(((2""-methoxyethoxy)methoxy)methyl)-2,8-dimethyldodec-8-en-3-ol

Formula: $C_{42}H_{68}O_{12}$

Molecular weight: 765.0 g/mol

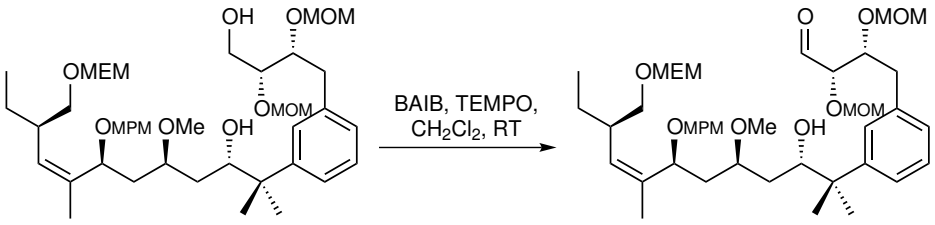
R_f: 0.18 (hexane/acetone 7/3)

ESI-MS (m/z): 609.2 ($M+OAc^-$)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.23-7.17 (m, 5H), 7.04 (app. dt, J = 6.6, 1.8 Hz, 1H), 6.86 (app. d, 8.7 Hz, 2H), 5.17 (app. dd, 10.4, 1.6 Hz, 1H), 4.81 (d, 6.9 Hz, 1H), 4.69 (d, 6.7 Hz, 1H, A part of AB-spinsystem), 4.68 (d, J = 6.7 Hz, 1H, B part of AB-spinsystem), 4.67 (d, J = 7.0 Hz, 1H), 4.51 (d, J = 6.9 Hz, 1H), 4.35 (d, J = 11.1 Hz, 1H), 4.34 (d, J = 7.1 Hz, 1H), 4.29 (dd, J = 9.7, 3.5 Hz, 1H), 4.07 (d, J = 11.2 HZ, 1H), 3.94 (ddd, J = 8.4, 5.4, 3.1 Hz, 1H), 3.85-3.80 (m, 1H), 3.80 (s, 3H), 3.79-3.70 (m, 2H), 3.69-3.65 (m, 2H), 3.57 (ddd, J = 6., 4.7, 3.2 Hz, 1H), 3.56-3.50 (m, 3H), 3.49 (dd, J = 9.5, 6.0 Hz, 1H), 3.46 (s, 3H), 3.41 (dd, J = 9.6, 6.9 Hz, 1H), 3.37 (s, 3H), 3.24 (s, 3H), 3.21 (s, 3H), 2.91 (dd, J = 13.6, 5.4 Hz, 1H), 2.84 (dd, J = 13.6, 8.4 Hz, 1H), 2.70 (d, J = 3.5 Hz, 1H), 2.59-2.51 (m, H), 2.15 (dd, J = 14.3, 9.8, 4.5 Hz, 1H), 1.70 (d, J = 1.4 Hz, 3H), 1.55-1.35 (m, 4H), 1.25 (s, 3H), 1.24-1.17 (m, 1H), 1.22 (s, 3H), 0.83 (app. t, J = 7.5 Hz, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 159.28 (C), 147.83 (C), 138.11 (C), 136.26 (C), 131.46 (CH), 130.98 (C), 129.63 (2 x CH), 128.30 (CH), 128.00 (CH), 127.06 (CH), 124.82 (CH), 113.90 (2 x CH), 98.11 (CH_2), 97.06 (CH_2), 95.68 (CH_2), 82.48 (CH), 79.67 (CH), 77.23 (CH), 76.00 (CH), 73.22 (CH), 71.93 (CH_2), 71.43 (CH_2), 69.66 (CH_2), 66.88 (CH_2), 62.99 (CH_2), 59.18 (CH_3) 56.48 (CH_3), 56.13 (CH_3), 55.99 (CH_3), 55.43 (CH_3), 42.43 (C), 39.24 (CH), 37.60 (CH_2), 36.62 (CH_2), 34.11 (CH_2), 25.29 (CH_2), 24.40 (CH_3), 23.92 (CH_3), 18.11 (CH_3), 11.84 (CH_3)

5.10.7 Synthesis of aldehyde 3.54



3.53 **3.54**

To a solution of **3.53** (90 mg, 118 μmol, 1 eq.) in CH_2Cl_2 (2.35 ml) were added bisacetoxyiodobenzene (BAIB) (49 mg, 153 μmol, 1.3 eq.) and (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO) (3.7 mg, 24 μmol, 0.2 eq.) at 0°C. The mixture was then stirred at RT for 19h, after which TLC-analysis (hexane/ acetone 7/3) showed complete conversion of the starting material. The reaction was quenched by adding a saturated aqueous solution of $Na_2S_2O_3$ (7.5 ml), and transferred to a separation funnel, containing a pH 4 buffer solution (7.5 ml) with CH_2Cl_2 (12 ml). The phases were separated, the aqueous phase was extracted with CH_2Cl_2 (4 x 15 ml), dried over $MgSO_4$ and concentrated. It was used without further purification for the next reaction.

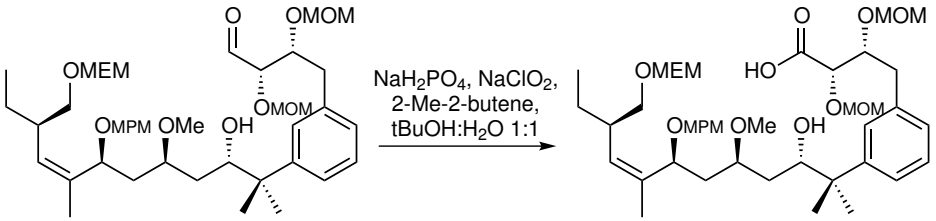
Name: (2*S*,3*R*)-4-(3'-((3"*S*,5"*S*,7"*S*,10"*R*,8*Z*)-3"-hydroxy-5"-methoxy-7"-((4"'-methoxybenzyl)oxy)-10"-(((2""-methoxyethoxy)methoxy)methyl)-2",8"-dimethyldodec-8"-en-2"-yl)phenyl)-2,3-bis(methoxymethoxy)butanal

Formula: $C_{42}H_{66}O_{12}$

Molecular weight: 763.0 g/mol

R_f: 0.40 (hexane/acetone 7/3)

5.10.8 Synthesis of carboxylic acid 3.55



3.54 **3.55**

Compound **3.54** (90 mg, 118 μmol, 1 eq.) was dissolved in *t*BuOH (17.6 ml) and 2-methyl-2-butene (2.3 ml) was added. Next, a solution of NaH_2PO_4 (197 mg, 1.65 mmol, 14 eq.) and $NaClO_2$ (226 mg, 2 mmol, 80%, 17 eq.) in water (17.6 ml) was added at room temperature and the mixture was stirred for 1h40', after which TLC-analysis (hexane/acetone 7/3) showed complete conversion of the starting material. The reaction mixture was poured in a pH 4 buffer solution (40 ml), extracted with CH_2Cl_2 (5 x 40 ml), dried over $MgSO_4$, and concentrated. The reaction mixture was not further purified, and used as such in the next reaction.

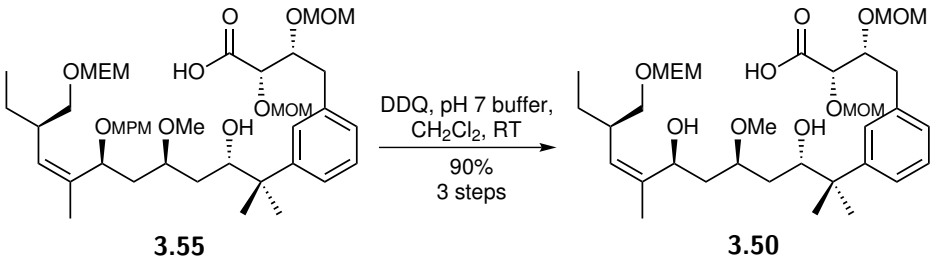
Name: (2*S*,3*R*)-4-(3'-((3"*S*,5"*S*,7"*S*,10"*R*,8*Z*)-3"-hydroxy-5"-methoxy-7"-((4"'-methoxybenzyl)oxy)-10"-(((2""-methoxyethoxy)methoxy)methyl)-2",8"-dimethyldodec-8"-en-2"-yl)phenyl)-2,3-bis(methoxymethoxy)butanoic acid

Formula: $C_{42}H_{66}O_{13}$

Molecular weight: 779.0 g/mol

R_f: 0.22 (CH_2Cl_2/MeOH/AcOH 95/5/1)

5.10.9 Alternative synthesis for carboxylic acid 3.50

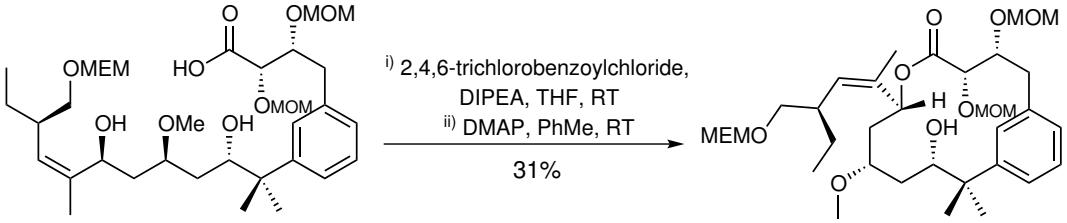


3.55 **3.50**

To a solution of **3.55** (92 mg, 118 μmol, 1 eq.) in CH_2Cl_2 (23.5 ml) and pH 7 phosphate buffer (3.8 ml) was added DDQ (134 mg, 0.59 mmol, 5 eq.) in one portion at room temperature. The solution was stirred at that temperature for 4h, after which TLC-analysis (CH_2Cl_2/MeOH/AcOH 95/5/1) showed complete conversion of the starting material. The reaction was quenched using a saturated aqueous solution of $NaHCO_3$ (5 ml) and water (10 ml) and acidified using 0.1M HCl until pH paper indicated pH 4 (50 ml). The mixture was then transferred to a separation funnel with CH_2Cl_2 (20 ml) and extracted with CH_2Cl_2 (4 x 40 ml). The combined organic phases were dried over $MgSO_4$ and concentrated. Flash column chromatography (CH_2Cl_2/MeOH/AcOH 96/4/1) provided *seco*-acid **3.50** as a white solid (70 mg, 90% over three steps).

The spectral data were in perfect agreement with the previously reported ones.

5.10.10 Synthesis of macrolactone 3.51



3.50 **3.51**

To a solution of *seco*-acid **3.50** (14 mg, 21 μmol, 1 eq.) in THF (0.65 ml) was added diisopropylethylamine (28 μl, 160 μmol, 7.5 eq.) and 2,4,6-trichlorobenzoyl-chloride (17 μl, 106 μmol, 5 eq.) at RT. The reaction mixture was stirred for 4h,

after which the solvent was evaporated *in vacuo*. The remnants were dissolved in toluene (4 ml) and added to a solution of 4-dimethylaminopyridine (65 mg, 531 μmol, 25 eq.) in toluene (32 ml) over 12h, using a syringe pump. After the addition, the syringe was rinsed with toluene (3 x 0.3 ml). The reaction was followed using TLC-analysis (CH2Cl2/ MeOH/ AcOH 95/5/0.5), and as it progressed, a white precipitation was formed. After 25h, the reaction was quenched using diluted HCl (30 ml, 0.1 M), the phases were separated, and the aqueous phase was extracted with EtOAc (3 x 40 ml). The organic phases were combined, dried over $MgSO_4$, and concentrated. Flash column chromatography (hexane/acetone 8/2) delivered the macrolide **3.51** (5mg, 8 μmol, 36%) as a clear oil.

Name: (1'*Z*,3*R*,3'*R*,4*S*,7*R*,9*S*,11*S*)-11-hydroxy-3,4-bis(Methoxymethoxy)-7-[3'-(2"-methoxyethoxymethoxymethyl)-1'-methylpent-1'-enyl]-9-methoxy-12,12-dimethyl-6-oxabicyclo[11.3.1]heptadeca-1(17),13,15-trien-5-one

Formula: $C_{34}H_{56}O_{11}$

Molecular weight: 640.8 g/mol

R_f: 0.17 (hexane/acetone 8/2)

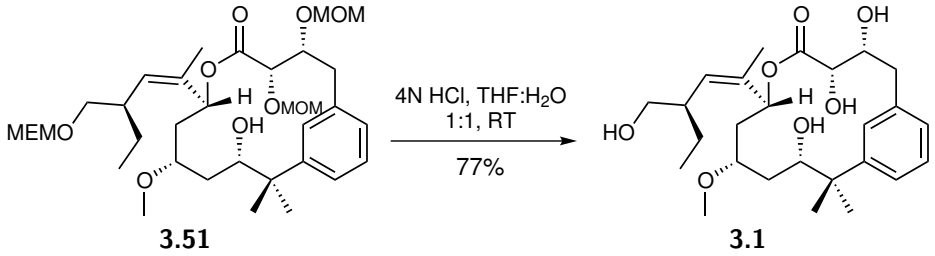
ESI-MS (m/z): 658.3 ($M+Na^+$)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.44 (app. d, J = 7.9 Hz, 1H), 7.29 (app. t, J = 7.7 Hz, 1H), 7.21 (app. t, J = 1.8 Hz, 1H), 7.17 (app. d, J = 7.5 Hz, 1H), 5.50 (dd, J = 10.8, 2.0 Hz, 1H), 5.01 (dd, J = 10.4, 1.4 Hz, 1H), 4.88 (d, J = 7.0 Hz, 1H, A part of AB-spinsystem 1), 4.83 (d, J = 7.0 Hz, 1H, B part of AB-spinsystem 1), 4.70 (d, J = 6.7 Hz, 1H, A part of AB-spinsystem 2), 4.69 (d, J = 6.8 Hz, 1H, B part of AB-spinsystem 2), 4.63 (d, J = 6.8 Hz, 1H, A part of AB-spinsystem 3), 4.59 (d, J = 6.8 Hz, 1H, B part of AB-spinsystem 3), 4.06 (ddd, J = 9.4, 5.6, 2.4 Hz, 1H), 4.03 (d, J = 5.7 Hz, 1H), 3.72-3.64 (m, 3H), 3.58-3.54 (m, 2H), 3.50-3.45 (m, 1H), 3.47 (s, 3H), 3.41-3.36 (m, 1H), 3.41 (s, 3H), 3.40 (s, 3H), 3.14 (dd, J = 14.1, 2.1 Hz, 1H), 2.97 (s, 3H), 2.94 (dd, J = 14.1, 9.3 Hz, 1H), 2.77-2.71 (m,

1H), 2.65-2.57 (m, 1H), 1.96 (ddd, J = 14.7, 10.6, 1.0 Hz, 1H), 1.65-1.50 (m, 2H), 1.63 (d, J = 1.4 Hz, 3H), 1.42 (s, 3H), 1.40 (s, 3H), 1.30-1.24 (m, 1H), 1.19-1.10 (m, 1H), 0.82 (app. t, J = 7.5 Hz, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 169.41 (C), 146.36 (C), 137.65 (C), 134.09 (C), 130.86 (CH), 128.71 (CH), 128.04 (CH), 127.63 (CH), 126.03 (CH), 96.90 (CH_2), 96.09 (CH_2), 95.68 (CH_2), 80.06 (CH), 78.17 (CH), 77.85 (CH), 75.51 (CH), 71.97 (CH_2), 70.89 (CH_2), 70.48 (CH), 66.77 (CH_2), 59.15 (CH_3), 56.20 (CH_3), 55.95 (CH_3), 55.90 (CH_3), 42.44 (C), 39.91 (CH), 38.87 (CH_2), 36.58 (CH_2), 36.25 (CH_2), 26.22 (CH_3), 25.69 (CH_3), 25.07 (CH_2), 18.29 (CH_3), 12.15 (CH_3)

5.10.11 Synthesis of pelofen B (3.1)



3.51 **3.1**

To a solution of macrolide **3.51** (5 mg, 8 μmol, 1 eq.) in THF (1ml) was added HCl (1ml, 4M) and the solution was stirred overnight at RT. The solution was then cooled to 0°C and neutralized using solid $NaHCO_3$. After the addition of a saturated aqueous solution of $NaHCO_3$ (5 ml), the mixture was transferred to a separation funnel using EtOAc (5 ml). The phases were separated and the aqueous phase is extracted with EtOAc (4 x 5 ml). The combined organic phases were dried over $MgSO_4$, and concentrated. Flash column chromatography (hexane/acetone 6/4) delivered pelofen **3.1** (3 mg, 6 μmol, 77%) as a white solid.

Name: (1'*Z*,3*R*,3'*R*,4*S*,7*R*,9*S*,11*S*)-3,4,11-trihydroxy-7-[3'-(hydroxymethylene)-1'-methylpent-1'-enyl]-9-methoxy-12,12-dimethyl-6-oxabicyclo[11.3.1]heptadeca-1(17),13,15-trien-5-one

Formula: $C_{26}H_{40}O_7$

Molecular weight: 464.6 g/mol

R_f: 0.26 (pentane/acetone 6/4)

$[\alpha]_D$: -17.0° (c = 1 mg/ml in $CDCl_3$)

ESI-MS (m/z): 465.2 ($M+H^+$)

HR-MS: calculated for ($M+H^+$) 465.2847, found 465.2851 (Δ 0.9 ppm)

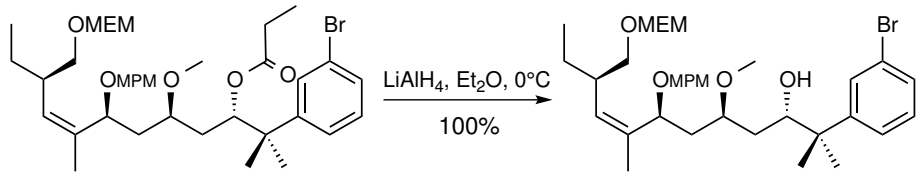
^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.38 (app. bs, 1H), 7.28-7.21 (m, 2H), 7.03 (app. dt, J = 6.9, 1.6 Hz, 1H), 5.44 (dd, J = 10.8, 3.4 Hz, 1H), 4.96 (app. d, J = 10.5 Hz, 1H), 4.32 (app. dd, J = 12.1, 5.0 Hz, 1H), 3.70-3.65 (m, 1H), 3.57 (dd, J = 10.6, 3.8 Hz, 1H), 3.50 (dd, J = 11.2, 2.3 Hz, 1H), 3.43 (app. s, 1H), 3.32-3.25 (m, 1H), 3.27 (s, 3H), 3.20 (dd, J = 12.7, 4.7 Hz, 1H), 2.92 (bs, 2H), 2.70 (app. t, J = 12.3 Hz, 1H), 2.48-2.38 (m, 1H), 1.93 (ddd, J = 15.3, 7.1, 3.4 Hz, 1H), 1.86 (app. dd, J = 15.3, 10.8 Hz, 1H), 1.68 (d, J = 1.4 Hz, 3H), 1.59-1.52 (m, 1H), 1.49 (s, 3H), 1.42-1.34 (m, 1H), 1.36 (s, 3H), 1.30 (app. ddd, J = 14.3, 11.4, 2.8 Hz, 1H), 1.16-1.07 (m, 1H), 0.84 (app. t, J = 7.4 Hz, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 174.23 (C), 146.83 (C), 137.03 (C), 136.99 (C), 130.40 (CH), 129.25 (CH), 128.55 (CH), 127.87 (CH), 124.86 (CH), 76.66 (CH), 74.93 (CH), 74.24 (CH), 73.90 (CH), 68.93 (CH), 67.16 (CH_2), 57.42 (CH_3), 43.44 (CH), 42.59 (C), 40.97 (CH_2), 38.69 (CH_2), 35.05 (CH_2), 26.47 (CH_3), 24.66 (CH_2), 21.17 (CH_3), 18.07 (CH_3), 12.33 (CH_3)

IR (HATR): 3450, 2955, 2926, 2871, 1735 (s), 1449, 1384, 1218, 1161, 1119, 1088, 1069, 962, 907, 797, 712 cm^{-1}

5.11 Synthesis of the 2,3-dideoxy analog

5.11.1 Synthesis of alcohol 3.68



3.26 **3.68**

To a cooled (0°C) suspension of $LiAlH_4$ (152 mg, 4.01 mmol, 3 eq.) in Et_2O (32 ml) was added a solution of ester **3.26** (946 mg, 1.34 mmol, 1 eq.) in Et_2O (32 ml) using a double-ended needle. The solution was stirred for 1h at 0°C, upon which TLC-analysis (hexane/EtOAc 7/3) indicated full conversion of the starting material. The excess $LiAlH_4$ was quenched by adding EtOAc (10 ml). Then, a saturated aqueous solution of Rochelle's salt (25 ml) was added, and the resulting mixture was stirred for 1h at RT. The mixture was transferred to a separation funnel containing another portion of a saturated aqueous solution of Rochelle?s salt (25 ml), extracted with EtOAc (3 x 50 ml), dried over $MgSO_4$ and concentrated. Flash column chromatography (hexane/ acetone 8/2) delivered alcohol **3.68** (871 mg, 1.34 mmol, 100%) as a colorless oil.

Name: (3*S*,5*S*,7*S*,10*R*,8*Z*)-2-(3'-bromophenyl)-5-methoxy-7-((4"-methoxybenzyl) oxy)-10-(((2"'-methoxyethoxy)methoxy)methyl)-2,8-dimethyldodec-8-en-3-ol

Formula: $C_{34}H_{51}BrO_7$

Molecular weight: 651.7 g/mol

R_f: 0.40 (hexane/acetone 7/3)

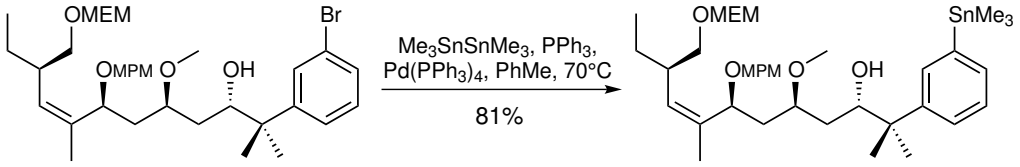
ESI-MS (m/z): 673.3 ($M+Na^+$)

HR-MS: calculated for ($M+Na^+$) 673.2710, found 673.2705 (Δ 0.8 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.49 (app. t, J = 1.9 Hz, 1H), 7.32 (ddd, J = 7.9, 2.0, 1.0 Hz, 1H), 7.29 (ddd, J = 7.9, 1.8, 1.0 Hz, 1H), 7.21 (app. d, J = 8.8 Hz, 2H), 7.16 (app. t, J = 7.9 Hz, 1H), 6.86 (app. d, J = 8.7 Hz, 2H), 5.17 (dd, J = 10.4, 1.6 Hz, 1H), 4.70 (d, J = 6.7 Hz, 1H, A part of AB-spinsystem), 4.69 (d, J = 6.7 Hz, 1H, B part of AB-spinsystem), 4.35 (d, J = 11.3 Hz, 1H), 4.24 (dd, J = 10.0, 3.3 Hz, 1H), 4.04 (d, J = 11.3 Hz, 1H), 3.81 (s, 3H), 3.81-3.78 (m, 1H), 3.69-3.66 (m, 2H), 3.56-3.50 (m, 3H), 3.50 (dd, J = 9.4, 5.9 Hz, 1H), 3.42 (dd, J = 9.5, 6.9 Hz, 1H), 3.37 (s, 3H), 3.25 (s, 3H), 2.97 (bs, 1H), 2.57-2.48 (m, 1H), 2.17 (ddd, J = 14.3, 10.1, 4.2 Hz, 1H), 1.71 (d, J = 1.5 Hz, 3H), 1.58-1.50 (m, 1H), 1.49 (ddd, J = 14.3, 7.8, 3.3 Hz, 1H), 1.43 (ddd, J = 14.8, 10.3, 4.6 Hz, 1H), 1.34 (ddd, J = 14.7, 5.9, 2.0 Hz, 1H), 1.24-1.17 (m, 1H), 1.23 (s, 3H), 1.22 (s, 3H), 0.83 (app. t, J = 7.5 Hz, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 159.31 (C), 150.10 (C), 136.19 (C), 131.54 (CH), 130.87 (C), 130.07 (CH), 129.72 (CH), 129.64 (2 x CH), 129.12 (CH), 125.63 (CH), 122.56 (C), 113.93 (2 x CH), 95.69 (CH_2), 77.33 (CH), 75.88 (CH), 73.08 (CH), 71.93 (CH_2), 71.47 (CH_2), 69.63 (CH_2), 66.89 (CH_2), 59.18 (CH_3), 56.55 (CH_3), 55.46 (CH_3), 42.64 (C), 39.31 (CH), 36.26 (CH_2), 33.53 (CH_2), 25.28 (CH_2), 24.53 (CH_3), 23.98 (CH_3), 18.12 (CH_3), 11.87 (CH_3)

5.11.2 Synthesis of stannane 3.79



3.68 **3.79**

In a pressure tube was added to a solution of alcohol **3.68** (873 mg, 1.34 mmol, 1 eq.) in toluene (13 ml), respectively hexamethylditin (555 μl, 2.68 mmol, 2 eq.), $AsPh_3$ (164 mg, 0.54 mmol, 0.4 eq.) and tetrakis(triphenylphosphine)palladium(0) (50 mg, 34 μmol, 3.3 mol%). The solution was heated to 70°C and stirred for 94h,

after which there was clear formation of Pd-black. Although TLC-analysis (hexane/acetone 8/2) did not show complete conversion, the reaction was quenched using a saturated aqueous solution of $NaHCO_3$ (15 ml) and water (15 ml). The aqueous phase was extracted with EtOAc (3 x 30 ml), dried over $MgSO_4$ and concentrated. Starting and target material were isolated together using flash column chromatography (hexane/ acetone 8/2). This mixture was then put back into reaction, using the same conditions as before. Every 20h fresh catalyst (50 mg, 34 μmol, 3.3 mol%) was added for 3 times. Quenching and workup was accomplished as described. After performing flash column chromatography, the mixture of starting and target material was put into reaction for a 3rd time, but now using 4 eq. of hexamethylditin, to prevent homo-coupling. Quenching and workup proceeded exactly as described earlier. Flash column chromatography (hexane/ acetone 9/1) now provided the stannane **3.79** (804 mg, 1.09 mmol, 81%) as a sticky oil.

Name: (3*S*,5*S*,7*S*,10*R*,8*Z*)-5-methoxy-7-((4'-methoxybenzyl)oxy)-10-(((2"-methoxyethoxy)methoxy)methyl)-2,8-dimethyl-2-(3"'-(trimethylstannyl)phenyl)-dodec-8-en-3-ol

Formula: $C_{37}H_{60}O_7Sn$

Molecular weight: 735.6 g/mol

R_f: 0.28 (hexane/acetone 8/2)

ESI-MS (m/z): 759.3 ($M+Na^+$)

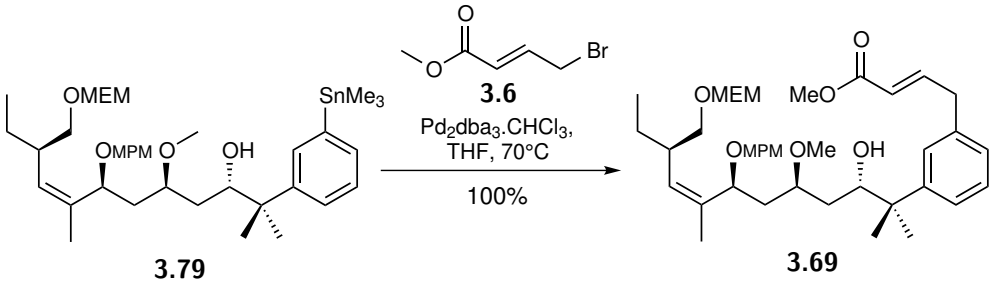
HR-MS: calculated for ($M+Na^+$) 759.3253, found 759.3251 (Δ 0.3 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.49-7.47 (m, 1H), 7.33-7.27 (m, 3H), 7.21 (app. d, J = 8.7 Hz, 2H) 6.85 (app. d, J = 8.7 Hz, 2H), 5.17 (dd, J = 10.5, 1.7 Hz, 1H), 4.70 (d, J = 6.7 Hz, 1H, A part of AB-spinsystem), 4.69 (d, J = 6.7 Hz, 1H, B part of AB-spinsystem), 4.34 (d, J = 11.3 Hz, 1H), 4.28 (dd, J = 9.6, 3.5 Hz, 1H), 4.06 (d, J = 11.3 Hz, 1H), 3.87 (dd, J = 10.1, 3.4 Hz, 1H), 3.80 (s, 3H), 3.68-3.65 (m, 2H), 3.56-3.50 (m, 3H), 3.49 (dd, J

= 9.3, 5.8 Hz, 1H), 3.42 (dd, J = 9.3, 6.8 Hz, 1H), 3.37 (s, 3H), 3.24 (s, 3H), 2.66 (d, J = 3.4 Hz, 1H), 2.60-2.51 (m, 1H), 2.15 (ddd, J = 14.4, 9.7, 4.5 Hz, 1H), 1.70 (d, J = 1.4 HZ, 3H), 1.56-1.46 (m, 3H), 1.41 (ddd, J = 14.4, 6.4, 2.1 Hz, 1H), 1.28 (s, 3H), 1.25 (s, 3H), 1.24-1.16 (m, 1H), 0.83 (app. t, J = 7.5 Hz, 3H), 0.27 (s, 9H, satellitepeaks: J = 27.5, 26.2 Hz)

APT (125 MHz; $CDCl_3$): δ (ppm) = 159.24 (C), 146.93 (C), 141.96 (C), 136.28 (C), 133.85 (CH), 133.60 (CH), 131.44 (CH), 131.00 (C), 129.62 (2 x CH), 127.84 (CH), 126.79 (CH), 113.90 (2 x CH), 95.69 (CH_2), 77.21 (CH), 76.05 (CH), 73.35 (CH), 71.93 (CH_2), 71.44 (CH_2), 69.71 (CH_2), 66.88 (CH_2), 59.18 (CH_3), 56.43 (CH_3), 55.43 (CH_3), 42.54 (C), 39.23 (CH), 36.75 (CH_2), 34.04 (CH_2), 25.29 (CH_2), 24.43 (CH_3), 23.73 (CH_3), 18.33 (CH_3), 11.85 (CH_3), -9.34 (3 x CH_3)

5.11.3 Synthesis of unsaturated ester 3.69



To a solution of stannane **3.79** (250 mg, 0.34 mmol, 1 eq.) in THF (1.7 ml) were added methyl-*E*-4-bromobutenoate (**3.6**) (81 μl, 0.68 mmol, 2 eq.) and $Pd_2(dba)_3 \cdot CHCl_3$ (5 mg, 5.1 μmol, 1.5 mol%) in a pressure tube and the resulting red-brown mixture was heated to 70°C, upon which it colored yellow. TLC-analysis (hexane/acetone 7/3) after 4h showed complete conversion of the starting material. The reaction was then quenched with a saturated aqueous solution of $NaHCO_3$ (15 ml), extracted with CH_2Cl_2 (4 x 15 ml), dried over $MgSO_4$ and concentrated. Flash column chromatography (hexane/acetone 8/2) yielded the unsaturated ester **3.69** (228 mg, 0.34 mmol, 100%) as a yellow oil.

Name: (3*S*,5*S*,7*S*,10*R*,8*Z*)-5-methoxy-7-((4'-methoxybenzyl)oxy)-10-(((2"-methoxyethoxy)methoxy)methyl)-2,8-dimethyl-2-(3"'-(trimethylstannyl)phenyl)-dodec-8-en-3-ol

Formula: $C_{39}H_{58}O_9$

Molecular weight: 670.9 g/mol

R_f: 0.14 (hexane/acetone 8/2)

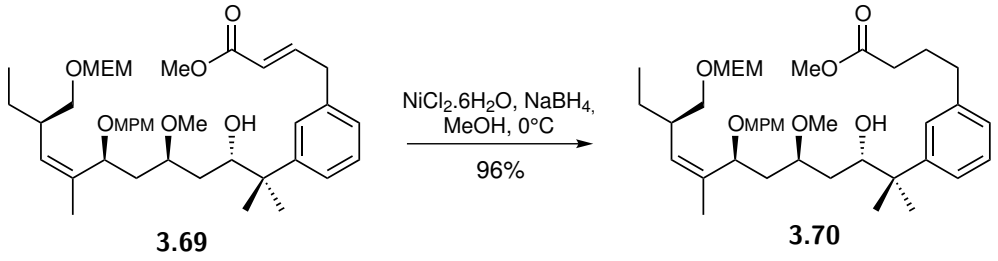
ESI-MS (m/z): 688.4 ($M+NH_4^+$)

HR-MS: calculated for ($M+Na^+$) 693.3973, found 693.3968 (Δ 0.7 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.25-7.19 (m, 4H), 7.16-7.14 (m, 1H), 7.09 (app. dt, J = 15.6, 6.9 Hz, 1H), 7.00-6.97 (m, 1H), 6.85 (app. d, J = 8.9 Hz, 2H), 5.81 (app. dt, J = 15.4, 1.7 Hz, 1H), 5.17 (app. dd, J = 10.4, 1.5 Hz, 1H), 4.70 (d, J = 6.7 Hz, 1H, A part of AB-spinsystem), 4.69 (d, J = 6.7 Hz, 1H, B part of AB-spinsystem), 4.35 (d, J = 11.4 Hz, 1H), 4.27 (dd, J = 9.8, 3.4 Hz, 1H), 4.05 (d, J = 11.3 Hz, 1H), 3.83 (ddd, J = 10.3, 3.4, 2.0 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.68-3.65 (m, 2H), 3.56-3.46 (m, 6H), 3.42 (dd, J = 9.4, 6.8 Hz, 1H), 3.37 (s, 3H), 3.23 (s, 3H), 2.80 (d, J = 3.4 Hz, 1H), 2.59-2.50 (m, 1H), 2.16 (ddd, J = 14.1, 9.6, 4.6 Hz, 1H), 1.70 (d, J = 1.6 Hz, 3H), 1.57-1.46 (m, 2H), 1.44 (ddd, J = 14.7, 10.2, 4.6 Hz, 1H), 1.36 (ddd, J = 14.5, 6.2, 2.0 Hz, 1H), 1.27-1.19 (m, 1H), 1.24 (s, 3H), 1.23 (s, 3H), 0.83 (app. t, J = 7.5 Hz, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 167.06 (C), 159.26 (C), 148.08 (C), 148.00 (CH), 137.36 (C), 136.25 (C), 131.46 (CH), 130.95 (C), 129.64 (2 x CH), 128.48 (CH), 127.29 (CH), 126.42 (CH), 125.21 (CH), 121.92 (CH), 113.90 (2 x CH), 95.68 (CH_2), 77.26 (CH), 76.01 (CH), 73.20 (CH), 71.92 (CH_2), 71.42 (CH_2), 69.64 (CH_2), 66.88 (CH_2), 59.17 (CH_3), 56.45 (CH_3), 55.42 (CH_3), 51.59 (CH_3), 42.44 (C), 39.24 (CH), 38.92 (CH_2), 36.53 (CH_2), 33.72 (CH_2), 25.28 (CH_2), 24.45 (CH_3), 23.97 (CH_3), 18.11 (CH_3), 11.83 (CH_3)

5.11.4 Synthesis of saturated ester 3.70



3.69 **3.70**

To a solution of unsaturated ester **3.69** (111 mg, 0.18 mmol, 1 eq.) in MeOH (3.6 ml), was added $NiCl_2 \cdot 6\,H_2O$ (1 mg, 0.7 mol, 4 mol%) and the red solution was cooled to 0°C. Then, $NaBH_4$ (14 mg, 0.36 mmol, 2 eq.) was added, gas started to evolve and the solution turned first brown, then black. After 10', TLC-analysis (hexane/acetone 8/2) showed complete conversion of the starting material, upon which the reaction mixture was filtered over Celite and concentrated. Flash column chromatography (hexane/acetone 8/2) yielded saturated ester **3.70** (116 mg, 0.17 mmol, 96%) as a colorless oil.

Name: Methyl 4-(3'-((3"*S*,5"*S*,7"*S*,10"*R*,8"*Z*)-3"-hydroxy-5"-methoxy-7"-((4"'-methoxybenzyl)oxy)-10"-(((2""-methoxyethoxy)methoxy)methyl)-2",8"-dimethyldodec-8"-en-2"-yl)phenyl) butanoate

Formula: $C_{39}H_{60}O_9$

Molecular weight: 672.9 g/mol

R_f: 0.3 (hexane/acetone 8/2)

$[\alpha]_D$: -48.2° (c: 7.3 mg/ml in $CHCl_3$)

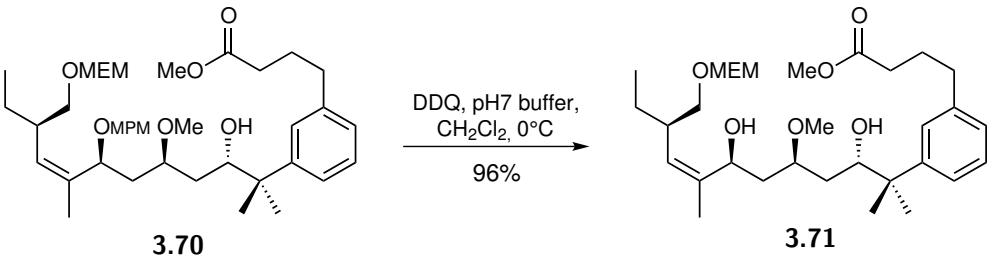
HR-MS: calculated for ($M+Na^+$) 695.4130, found 695.4115 (Δ 2.2 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = (7.23-7.16 (m, 5H), 7.00 (app. dt, J = 6.7, 1.8 Hz, 1H), 6.85 (app. d, J = 8.7 Hz, 2H), 5.17 (dd, J = 10.5, 1.6 Hz, 1H), 4.69 (d, J = 6.6 Hz, 1H, A part of AB-spinsystem), 4.68 (d, J = 6.6 Hz, 1H, B part of AB-spinsystem), 4.34 (d, J = 11.3 Hz, 1H), 4.28 (dd, J =

9.6, 3.5 Hz, 1H), 4.07 (d, J = 11.3 Hz, 1H), 3.85 (dd, J = 9.5, 2.8 Hz, 1H), 3.80 (s, 3H), 3.69-3.65 (m, 2H), 3.66 (s, 3H), 3.56-3.48 (m, 3H), 3.49 (dd, J = 9.5, 5.9 Hz, 1H), 3.42 (dd, J = 9.4, 6.7 Hz, 1H), 3.37 (s, 3H), 3.24 (s, 3H), 2.65-2.52 (m, 3H), 2.32 (app. t, J = 7.4 Hz), 2H), 2.15 (ddd, J = 14.4, 9.8, 4.5 Hz, 1H), 1.98-1.91 (m, 2H), 1.70 (d, J = 1.4 Hz, 3H), 1.56-1.37 (m, 4H), 1.27 (s, 3H), 1.25 (s, 3H), 1.24-1.18 (m, 1H), 0.84 (app. t, J = 7.5 Hz, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 174.05 (C), 159.34 (C), 147.70 (C), 141.14 (C), 136.38 (C), 131.41 (CH), 131.18 (C), 129.56 (2 x CH), 128.22 (CH), 127.08 (CH), 126.11 (CH), 124.52 (CH), 113.98 (2 x CH), 95.77 (CH_2), 77.26 (CH), 76.10 (CH), 73.49 (CH), 72.01 (CH_2), 71.54 (CH_2), 69.76 (CH_2), 66.98 (CH_2), 59.13 (CH_3), 56.41 (CH_3), 55.45 (CH_3), 51.56 (CH_3), 42.48 (C), 39.29 (CH), 36.95 (CH_2), 35.62 (CH_2), 34.23 (CH_2), 33.67 (CH_2), 26.79 (CH_2), 25.35 (CH_2), 24.54 (CH_3), 23.94 (CH_3), 18.10 (CH_3), 11.78 (CH_3)

5.11.5 Synthesis of alcohol 3.71



3.70 **3.71**

To a solution of ester **3.70** (68 mg, 102 μmol, 1 eq.) in CH_2Cl_2 (5 ml) and pH 7 phosphate buffer (0.5 ml) at 0°C was added 2,3-dichloro-5,6-dicyanobenzoquinone (115 mg, 508 μmol, 5 eq.) in one portion. The reaction mixture was stirred at 0°C for 2 h, after which TLC-analysis (hexane/acetone 8/2) showed complete conversion of the starting material. The reaction was quenched using a saturated aqueous solution of $NaHCO_3$ (5 ml) and water (5ml), diluted with CH_2Cl_2 (5 ml) and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 x 10 ml), the combined organic phases are dried over $MgSO_4$ and concentrated.

Flash column chromatography (hexane/acetone 8/2) provides **3.71** as a colorless oil (53 mg, 96 μmol, 96%).

Name: Methyl 4-(3'-((3"*S*,5"*S*,7"*S*,10"*R*,8"*Z*)-3",7"-dihydroxy-5"-methoxy-10"-(((2""-methoxyethoxy)methoxy)methyl)-2",8"-dimethyldodec-8"-en-2"-yl)-phenyl)butanoate

Formula: $C_{31}H_{52}O_8$

Molecular weight: 552.7 g/mol

R_f: 0.07 (hexane/acetone 8/2)

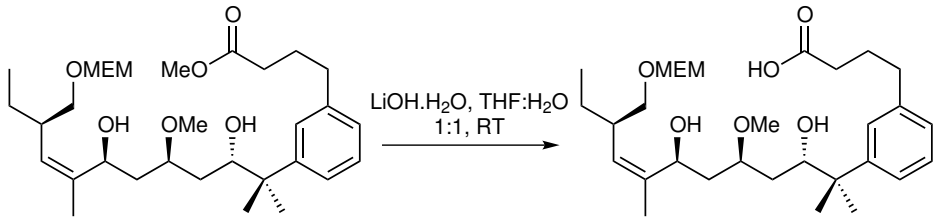
$[\alpha]_D$: -15.8° (c: 7.3 mg/ml in $CHCl_3$)

HR-MS: calculated for (M+Na^+) 575.3554, found 575.3550 (Δ 0.8 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.25-7.18 (m, 3H), 7.04-6.99 (m, 1H), 4.97 (dd, J = 10.1, 1.6 Hz, 1H), 4.68 (d, J = 6.8 Hz, 1H, A part of AB-spinsystem), 4.66 (d, J = 6.8 Hz, 1H, B part of AB-spinsystem), 4.57 (dd, J = 8.7, 4.6 Hz, 1H), 3.90 (dd, J = 10.2, 1.4 Hz, 1H), 3.67-3.61 (m, 2H), 3.65 (s, 3H), 3.56-3.44 (m, 4H), 3.38 (s, 3H), 3.29-3.23 (m, 1H), 3.28 (s, 3H), 3.00 (bs, 1H), 2.84 bs, 1H), 2.64-2.54 (m, 3H), 2.33 (app. t, J = 15.2 Hz, 2H), 2.03 (ddd, J = 14.4, 8.5, 6.9 Hz, 1H), 1.99-1.91 (m, 2H), 1.70 (d, J = 1.3 Hz, 3H), 1.62-1.38 (m, 4H), 1.33 (s, 3H), 1.32 (s, 3H), 1.23-1.12 (m, 1H), 0.84 (app. t, J = 7.5 Hz, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 174.11 (C), 147.49 (C), 141.19 (C), 139.60 (C), 130.67 (CH), 128.27 (CH), 127.02 (CH), 126.23 (CH), 124.42 (CH), 95.50 (CH_2), 78.66 (CH), 76.24 (CH), 71.90 (CH_2), 71.26 (CH_2), 67.02 (CH_2), 66.49 (CH), 59.15 (CH_3), 56.80 (CH_3), 51.66 (CH_3), 42.46 (C), 39.30 (CH), 37.27 (CH_2), 35.57 (CH_2), 34.25 (CH_2), 33.61 (CH_2), 26.78 (CH_2), 25.04 (CH_2), 24.51 (CH_3), 23.82 (CH_3), 18.30 (CH_3), 11.95 (CH_3)

5.11.6 Synthesis of carboxylic acid 3.72



3.71 **3.72**

To a solution of **3.71** (10 mg, 18 μmol, 1 eq.) in a mixture of THF (360 μl) and water (360 μl) is added $LiOH \cdot H_2O$ (7 mg, 180 μmol, 10 eq.) at RT. The reaction mixture was stirred overnight. TLC-analysis (hexane/ acetone 6/4) indicated complete conversion of the starting material. The reaction mixture was then poured into a saturated aqueous NH_4Cl solution (5 ml), extracted with EtOAc (5 x 5 ml), dried over $MgSO_4$ and concentrated. Dry toluene (1 ml) is added to the crude product and evaporated, yielding crude carboxylic acid **3.72** (10 mg, 18 μmol, 100%) as a clear oil, which is used without further purification.

Name: Methyl 4-(3'-((3"*S*,5"*S*,7"*S*,10"*R*,8"*Z*)-3",7"-dihydroxy-5"-methoxy-10"-(((2""-methoxyethoxy)methoxy)methyl)-2",8"-dimethyldodec-8"-en-2"-yl)-phenyl) butanoic acid

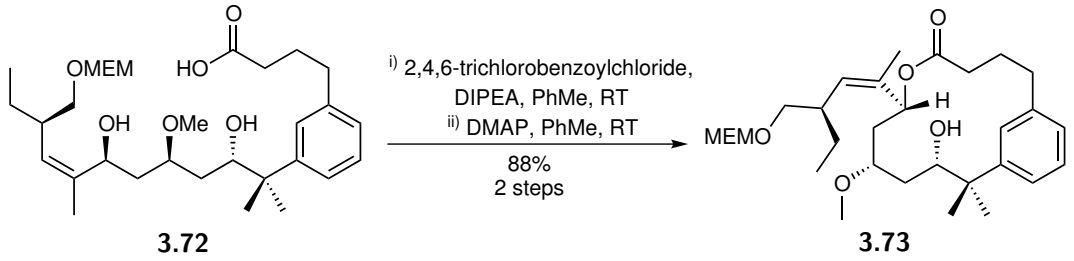
Formula: $C_{30}H_{50}O_8$

Molecular weight: 538.7 g/mol

R_f: 0.55 (CH_2Cl_2/MeOH/AcOH 95/5/1)

ESI-MS (m/z): 537.2 ($M\text{-}H^+$)

5.11.7 Synthesis of macrolactone 3.73



3.72 **3.73**

To a solution of the crude carboxylic acid **3.72** (10 mg, 18 μmol, 1 eq.) in PhMe (540 μl) were added consecutive DIPEA (24 μl, 135 μmol, 7.5 eq.) and 2,4,6-trichlorobenzoylchloride (14 μl, 90 μmol, 5 eq.) at RT. After 45' of anhydride formation, the reaction mixture was diluted with PhMe (5 ml), and sucked into a syringe. The flask was rinsed with PhMe (4.4 ml in 3 times) and everything was added to the same syringe. The solution containing the anhydride (10 ml total volume) was then added at RT over 12h (0.8 ml/h) to a solution of DMAP (55 mg, 450 mmol, 25 eq.) in PhMe (18 ml) using a syringe pump. 22h after the start of the addition, TLC-analyis (CH_2Cl_2/MeOH/AcOH 95/5/1) showed complete conversion of the starting material. The reaction was poured into diluted HCl (20 ml, 0.1 M) and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 30 ml), the combined organic phases were washed with a saturated aqueous $NaHCO_3$ solution (25 ml), dried over $MgSO_4$ and concentrated. Purification using flash column chromatography (hexane/acetone 88/12) delivered the macrocyclic ester **3.73** as a sticky oil (8 mg, 15 μmol, 88% over 2 steps).

Name: (3'R, 7S, 9R, 11S, 1'Z)-11-hydroxy-9-methoxy-7-(3'-(2"-methoxyethoxy-methoxymethyl)-1'-methylpent-1'-enyl)-12,12-dimethyl-6-oxabicyclo-[11.3.1]-heptadeca-1(17)-13,15-trien-5-one

Formula: $C_{30}H_{48}O_7$

Molecular weight: 520.7 g/mol

R_f: 0.39 (hexane/acetone 9/1)

$[\alpha]_D$: -72.7° (c:7.3 mg/ml in $CHCl_3$)

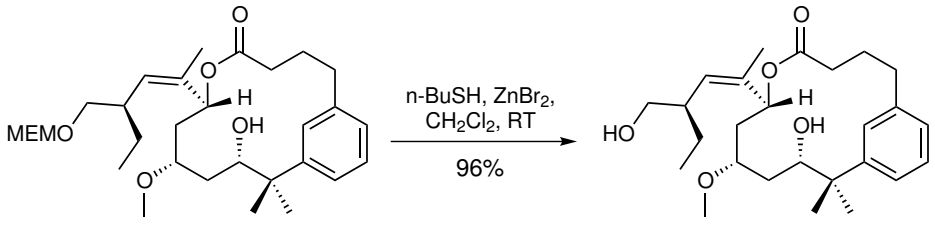
ESI-MS (m/z): 538.3 ($M+NH_4^+$)

HR-MS: calculated for ($M+NH_4^+$) 538.3738, found 538.3753 (Δ 2.8 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.28-7.23 (m, 2H), 7.06-7.01 (m, 2H), 5.52 (dd, J = 10.4, 1.3 Hz, 1H), 4.97 (dd, J = 10.4, 1.4 Hz, 1H), 4.704 (d, J = 6.9 Hz, 1H, A part of AB-spinsystem), 4.695 (d, J = 6.9 Hz, 1H, B part of AB-spinsystem), 3.79-3.74 (m, 1H), 3.74-3.64 (m, 2H), 3.61-3.54 (m, 2H), 3.50 (dd, J = 9.4, 5.0 Hz, 1H) 3.40 (s, 3H), 3.40-3.33 (m, 2H), 3.36 (dd, J = 9.4, 6.7 Hz, 1H), 3.23 (s, 3H), 2.88 (ddd, J = 13.5, 8.6, 4.7 Hz, 1H), 2.69-2.61 (m, 2H), 2.29-2.16 (m, 3H), 1.93 (ddd, J = 17.6, 10.3, 2.9 Hz, 1H), 1.89-1.79 (m, 2H), 1.66-1.50 (m, 3H), 1.57 (d, J = 1.5 Hz), 1.40 (s, 3H), 1.37 (s, 3H), 1.21-1.14 (m, 1H), 1.05 (ddd, J = 14.8, 8.5, 2.4 Hz, 1H), 0.81 (app. t, J = 7.5 Hz, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 171.70 (C), 145.84 (C), 139.91 (C), 135.04 (C), 129.67 (CH), 128.60 (CH), 127.90 (CH), 126.57 (CH), 124.84 (CH), 95.68 (CH_2), 77.03 (CH), 75.95 (CH), 72.00 (CH_2), 70.91 (CH_2), 68.37 (CH), 66.75 (CH_2), 59.15 (CH_3), 56.59 (CH_3), 42.38 (C), 39.36 (CH), 36.79 (CH_2), 35.55 (CH_2), 34.53 (CH_2), 31.49 (CH_2), 27.54 (CH_3), 25.16 (CH_2), 23.47 (CH_3), 23.22 (CH_2), 18.67 (CH_3), 11.84 (CH_3)

5.11.8 Synthesis of 2,3-dideoxy analog 3.74



3.73 **3.74**

To a solution of the MEM-ether **3.73** (7 mg, 13 μmol, 1 eq.) in CH_2Cl_2 (540 μl) was added *n*-BuSH (2 μl, 20 μmol, 1.5 eq.) and $ZnBr_2$ (5 mg, 20 μmol, 1.5

eq.) at RT. The reaction was followed using TLC-analysis (hexane/acetone 8/2) and stirred for 25', after which the mixture was poured into a saturated aqueous $NaHCO_3$ solution (5 ml). The mixture was extracted with CH_2Cl_2 (4 x 5 ml), dried over $MgSO_4$ and concentrated. Flash column chromatography (hexane/acetone 8/2) delivered the **3.74** as a white solid (5.5 mg, 12.5 μmol, 96%). Before submitting the sample to biological testing, it was extra purified using preparative HPLC (Luna C_{18} column, 50% MeCN to 100% MeCN in 30 minutes).

Name: (3'R, 7S, 9R, 11S, 1'Z)-11-hydroxy-9-methoxy-7-(3'-hydroxymethyl-1'-methylpent-1'-enyl)-12,12-dimethyl-6-oxabicyclo-[11.3.1]-heptadeca-1(17)-13,15-trien-5-one

Formula: $C_{26}H_{40}O_5$

Molecular weight: 432.6 g/mol

R_f: 0.19 (hexane/acetone 8/2)

$[\alpha]_D$: -53.7° (c: 5.6 mg/ml in $CHCl_3$)

ESI-MS (m/z): 450.3 ($M+NH_4^+$)

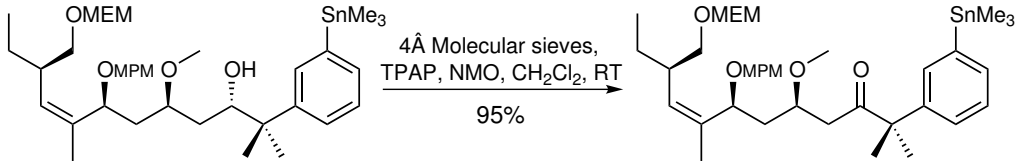
HR-MS: calculated for ($M+NH_4^+$) 433.2949, found 433.2958 (Δ 2.2 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.30-7.22 (m, 2H), 7.06-7.02 (m, 2H), 5.46 (dd, J = 10.5, 1.2 Hz, 1H), 4.91 (dd, J = 10.8, 1.5 Hz, 1H), 3.76 (dd, J = 8.9, 2.4 Hz, 1H), 3.63 (dd, J = 10.3, 4.1 Hz, 1H), 3.46-3.40 (m, 1H), 3.27 (s, 3H), 3.24 (app. t, J = 10.1 Hz, 1H), 2.83 (ddd, J = 13.7, 8.8, 4.6 Hz, 1H), 2.67-2.58 (m, 2H), 2.27 (ddd, J = 17.2, 6.8, 3.4, 1H), 2.24-2.15 (m, 1H), 1.96 (ddd, J = 17.2, 10.2, 3.3 Hz, 1H), 1.89 (ddd, J = 15.1, 10.4, 2.7 Hz, 1H), 1.88-1.80 (m, 1H), 1.65 (ddd, J = 15.1, 5.8, 1.5 Hz, 1H), 1.57 (d, J = 1.4 Hz, 3H), 1.50 (ddd, J = 14.8, 11.0, 2.4 Hz, 1H), 1.41 (s, 3H), 1.41-1.34 (m, 1H), 1.38 (s, 3H), 1.11-1.04 (m, 1H), 1.01 (ddd, J = 14.9, 8.9, 2.4 Hz, 1H), 0.82 (app. t, J = 7.4 Hz, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 173.27 (C), 145.74 (C), 139.84 (C), 136.10 (C), 131.24 (CH), 128.73 (CH), 128.10 (CH), 126.56 (CH), 124.79 (CH), 76.80 (CH), 75.80 (CH), 69.58 (CH), 66.85 (CH_2), 56.84 (CH_3), 42.71 (CH), 42.39 (C), 37.04 (CH_2), 35.34 (CH_2), 34.44 (CH_2), 31.55 (CH_2), 27.56 (CH_3), 24.80 (CH_2), 23.47 (CH_2), 23.07 (CH_3), 18.10 (CH_3), 12.05 (CH_3)

5.12 Ring-closing metathesis approach

5.12.1 Synthesis of ketone 3.84



3.79 **3.84**

To a flask, containing molecular sieves 4Å (408 mg) and *N*-methylmorpholine-*N*-oxide (60 mg, 0.49 mmol, 3 eq.), was added a solution of **3.79** (120 mg, 0.16 mmol, 1 eq.) in CH_2Cl_2 (8.16 ml). Next, tetrapropylammonium perruthenate (4.5 mg, 0.013 mmol, 0.075 eq.) was added in one portion and the reaction mixture was stirred at RT for 24h, after which TLC-analysis (hexane/acetone 9/1) showed complete conversion of the starting material. The reaction mixture was filtered over a P4 filter and to the filtrate a saturated aqueous solution of NH4Cl (8 ml) and water (8ml) were added. The isolated organic phase was dried over $MgSO_4$, concentrated and purified using flash column chromatography (hexane/EtOAc 8/2), yielding **3.84** (113 mg, 95 %).

Name: (5*R*,7*S*,10*R*,8*Z*)-5-methoxy-7-((4'-methoxybenzyl)oxy)-10-(((2"-methoxyethoxy)methoxy)methyl)-2,8-dimethyl-2-(3"'-(trimethylstannyl)phenyl)dodec-8-en-3-one

Formula: $C_{37}H_{58}O_7Sn$

Molecular weight: 733.6 g/mol

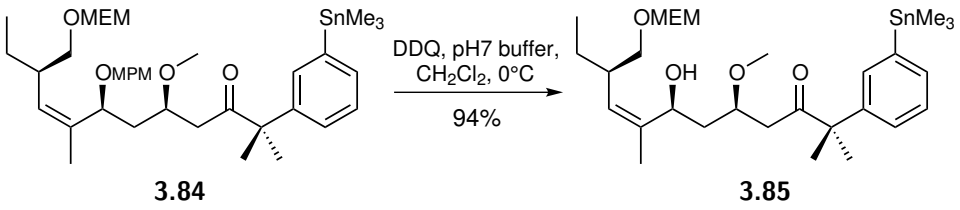
R_f: 0.28 (hexane/acetone 9/1)

HR-MS: calculated for ($M+NH_4^+$) 752.3543, found 752.3539 (Δ 0.5 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.35 (app. dt, J = 7.1, 1.1 Hz, 1H), 7.33-7.25 (m, 2H), 7.17 (app. d, J = 8.7 Hz, 2H), 7.12 (ddd, J = 7.8, 2.2, 1.2 Hz, 1H), 6.84 (app. d, J = 8.7 Hz, 2H), 5.17 (app.dd, J = 10.4, 1.5 Hz, 1H), 4.68 (d, J = 6.7 Hz, 1H, A part of AB-spinsystem), 4.67 (d, J = 6.7 Hz, 1H, B part of AB-spinsystem), 4.32 (d, J = 11.1 Hz, 1H), 4.22 (dd, J = 8.7, 4.3 Hz, 1H), 4.08 (d, J = 11.2, 1H), 3.83-3.77 (m, 1H), 3.80 (s, 3H), 3.68-3.64 (m, 2H), 3.55-3.52 (m, 2H), 3.46 (dd, J = 9.4, 5.8 Hz, 1H), 3.39 (dd, J = 9.4, 6.6 Hz, 1H), 3.37 (s, 3H), 2.53 (dd, J = 17.3, 7.5 HZ, 1H), 2.50-2.42 (m, 1H), 2.20 (dd, J = 17.3, 4.8 Hz, 1H), 1.87 (ddd, J = 14.2, 8.8, 5.3 Hz, 1H), 1.68 (d, J = 1.4 Hz, 3H), 1.49-1.40 (m, 2H), 1.46 (s, 3H), 1.42 (s, 3H), 1.16 (ddt, J = 15.2, 13.5, 7.6 Hz, 1H), 0.74 (app. t, J = 7.5 Hz, 3H), 0.26 (s, 9H, satellitepeaks: d, J(^{1}H-^{119}Sn) = 55.2 Hz, d, J(^{1}H-^{117}Sn) = 52.7 Hz)

APT (125 MHz; $CDCl_3$): δ (ppm) = 211.70 (C), 159.12 (C), 143.46 (C), 142.90 (C), 136.08 (C), 134.42 (CH), 133.41 (CH), 131.59 (CH), 131.25 (C), 129.49 (2 x CH), 128.30 (CH), 126.28 (CH), 113.84 (2 x CH), 95.67 (CH_2), 74.70 (CH), 73.23 (CH), 71.92 (CH_2), 71.38 (CH_2), 69.54 (CH_2), 66.85 (CH_2), 59.17 (CH_3), 56.72 (CH_3), 55.42 (CH_3), 52.54 (C), 42.35 (CH_2), 39.05 (CH), 37.82 (CH_2), 25.38 (CH_3), 25.30 (CH_3), 25.23 (CH_2), 18.03 (CH_3), 11.74 (CH_3), -9.37 (3 x CH_3)

5.12.2 Synthesis of stannane 3.85



3.84 **3.85**

To a solution of **3.84** (96 mg, 0.13 mmol, 1 eq.) in CH2Cl2 (6.5 ml) were added a pH 7 phosphate buffer (0.65 ml) and DDQ (149 mg, 0.65 mmol, 5 eq.) at 0°C. The reaction mixture was stirred for 1h at that temperature, after which TLC-analysis (hexane/EtOAc) showed complete conversion of the starting material. The reaction mixture was transferred to a separation funnel containing water (10 ml) and a saturated aqueous solution of $NaHCO_3$ (10 ml), and extracted with CH_2Cl_2 (4 x 20 ml). After drying over $MgSO_4$, the product was purified using gradual flash column chromatography (hexane/acetone 9/1 to 8/2), providing **3.85** (75 mg, 94%).

Name: (5*R*,7*S*,10*R*,8*Z*)-5-methoxy-7-hydroxy-10-(((2"-methoxyethoxy)methoxy)-methyl)-2,8-dimethyl-2-(3"'-(trimethylstannyl)phenyl)dodec-8-en-3-one

Formula: $C_{29}H_{50}O_6Sn$

Molecular weight: 613.4 g/mol

R_f: 0.32 (hexane/acetone 8/2)

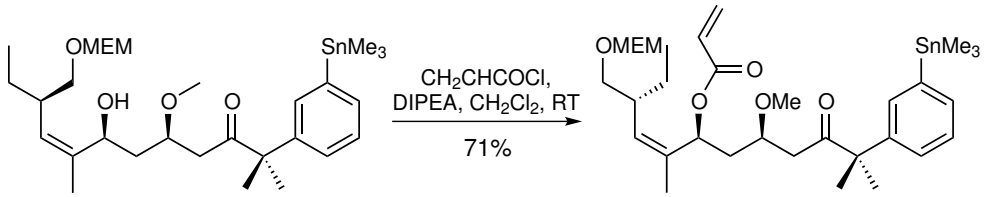
HR-MS: calculated for ($M+Na^+$) 637.2522, found 637.2523 (Δ 0.2 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.38 (app. dt, J = 7.1, 1.1 Hz, 1H), 7.35-7.33 (m, 1H), 7.31 (app. t, J = 7.4 Hz, 1H), 7.19 (ddd, J = 7.8, 2.2, 1.3 Hz), 4.98 (app. dd, J = 10.1, 1.5 Hz, 1H), 4.68 (d, J = 6.8 Hz, 1H, A part of AB-spinsystem), 4.67 (d, J = 6.8 Hz, 1H, B part of AB-spinsystem), 4.60 (app. t, J = 6.6 Hz, 1H), 3.71-3.63 (m, 3H), 3.56-3.53 (m, 2H), 3.50 (dd, J = 9.3, 5.0 Hz, 1H), 3.38 (s, 3H), 3.28 (dd, J = 9.0, 8.6 Hz, 1H), 2.96 (d, J = 1.5 Hz, 1H), 2.64-2.55 (m, 1H), 2.61 (dd, J = 17.2, 5.2 Hz, 1H), 2.30 (dd, J = 17.2, 7.1 Hz, 1H), 1.71 (d, J = 1.5 Hz, 3H), 1.68-1.59 (m, 1H), 1.54-1.40 (m, 2H), 1.50 (s, 3H), 1.48 (s, 3H), 1.23-1.13 (m, 2H), 0.84 (app. t, J = 7.5 Hz, 3H), 0.28 (s, 9H, satellitepeaks: d, J(^{1}H-^{119}Sn) = 55.2 Hz, d, J(^{1}H-^{117}Sn) = 52.8 Hz)

APT (125 MHz; $CDCl_3$): δ (ppm) = 211.68 (C), 143.16 (C), 143.03 (C), 139.40 (C), 134.62 (CH), 133.37 (CH), 130.56 (CH), 128.42 (CH), 126.24 (CH), 95.54

(CH_2), 76.59 (CH), 71.91 (CH_2), 71.34 (CH_2), 67.17 (CH), 66.96 (CH_2), 59.15 (CH_3), 56.96 (CH_3), 52.71 (C), 42.28 (CH_2), 39.24 (CH), 39.03 (CH_2), 25.20 (CH_3), 25.16 (CH_3), 25.10 (CH_2), 18.15 (CH_3), 11.96 (CH_3), -9.33 (3 x CH_3)

5.12.3 Synthesis of ester 3.86



3.85 **3.86**

To a solution of **3.85** (35.6 mg, 58 μmol, 1 eq.) in CH_2Cl_2 (0.58 ml) was added DIPEA (0.15 ml, 0.87 mmol, 15 eq.) and the mixture was cooled to 0°C. Then, acryloyl chloride (5.8 ml, 0.58 mmol, 10 eq., 0.1 M solution in CH_2Cl_2) was added and the reaction mixture was stirred for 1h at 0°C, then warmed to RT and stirred further for 2h. TLC-analysis (hexane/ acetone 8/2) did not show complete conversion of the starting material, but the reaction was quenched anyway by addition of a saturated aqueous solution of NH4Cl (10 ml). The reaction was extracted with CH_2Cl_2 (4 x 10 ml), dried over $MgSO_4$ and concentrated. Flash column chromatography deliverd **3.86** (27.4 mg, 71%) as a clear oil. Also the non-reacted starting material could be recuperated (6 mg, 84% yield based on recovered starting material).

Name: (5*R*,7*S*,10*R*,8*Z*)-2'-(3"-(trimethylstannyl)phenyl)-3'-oxo-2',8'-dimethyl-10'-(((2"'-methoxyethoxy)methoxy)methyl)-dodec-8'-en-7'-yl butenoate

Formula: $C_{32}H_{52}O_7Sn$

Molecular weight: 667.5 g/mol

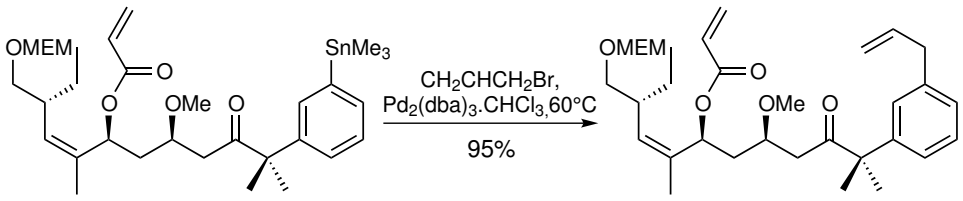
R_f: 0.48 (hexane/acetone 8/2)

HR-MS: calculated for ($M+NH_4^+$) 686.3073, found 686.3069 (Δ 0.6 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.36 (app. dt, J = 7.1, 1.1 Hz, 1H), 7.32-7.28 (m, 2H), 7.18 (ddd, J = 7.8, 2.1, 1.3 Hz, 1H), 6.29 (dd, J = 17.3, 1.5 Hz, 1H), 6.01 (dd, J = 17.3, 10.4 Hz, 1H), 5.76 (dd, J = 7.8, 6.1 Hz, 1H), 5.74 (dd, J = 10.4, 1.5 Hz, 1H), 5.14 (dq, J = 10.2, 1.5 Hz, 1H), 4.65 (app. s, 2H), 3.69-3.61 (m, 3H), 3.55-3.52 (m, 2H), 3.44 (dd, J = 9.5, 5.6 Hz, 1H), 3.40 (dd, J = 9.5, 6.1 Hz, 1H), 3.38 (s, 3H), 3.13 (s, 3H), 2.69-2.61 (m, 1H), 2.58 (dd, J = 17.3, 6.1 Hz, 1H), 2.25 (dd, J = 17.3, 6.3 Hz, 1H), 1.83 (app. dt, J = 14.4, 7.3 Hz, 1H), 1.71 (d, J = 1.5 Hz, 3H), 1.63 (ddd, J = 14.3, 6.1, 4.8 Hz, 1H), 1.56-1.50 (m, 1H), 1.48 (s, 3H), 1.46 (s, 3H), 1.27-1.17 (m, 1H), 0.82 (app. t, J = 7.5 Hz, 3H), 0.28 (s, 9H, satellitepeaks: d, J(^{1}H-^{119}Sn) = 55.5 Hz, d, J(^{1}H-^{117}Sn) = 52.8 Hz)

APT (125 MHz; $CDCl_3$): δ (ppm) = 211.42 (C), 165.01 (C), 143.12 (C), 143.07 (C), 134.57 (CH), 133.77 (C), 133.39 (CH), 132.07 (CH), 130.34 (CH_2), 129.02 (CH), 128.44 (CH), 126.17 (CH), 95.62 (CH_2), 74.44 (CH), 71.97 (CH_2), 70.67 (CH_2), 70.15 (CH), 66.70 (CH_2), 59.12 (CH_3), 56.46 (CH_3), 52.64 (C), 41.75 (CH_2), 39.32 (CH), 37.09 (CH_2), 25.43 (CH_3), 25.09 (CH_2), 25.03 (CH_3), 18.62 (CH_3), 11.76 (CH_3), -9.35 (3 *x* CH_3)

5.12.4 Synthesis of diene 3.87



3.86 **3.87**

In a pressure tube containing **3.86** (27.4 mg, 41 μmol, 1 eq.) in pure allylbromide (0.41 ml) was added $Pd_2(dba)_3 \cdot CHCl_3$ (2mg, 2 μmol, 0.05 eq.) and the reaction mixture was heated to 60°C. After 45', TLC analysis (Hexane/EtOAc 8/2) showed complete conversion of the starting material, and the reaction mixture was poured in water (10 ml), extracted with Et_2O (4 x 10 ml), dried over

MgSO4 and concentrated. Purification by means of flash column chromatography (hexane/EtOAc 8/2) provided diene **3.87** (21 mg, 95%) as a colorless oil.

Name: (5*R*,7*S*,10*R*,8*Z*)-2'-(3"-(prop-2"'-ene)phenyl)-3'-oxo-2',8'-dimethyl-10'-(((2""-methoxyethoxy)methoxy)methyl)-dodec-8'-en-7'-yl butenoate

Formula: $C_{32}H_{48}O_7$

Molecular weight: 544.7 g/mol

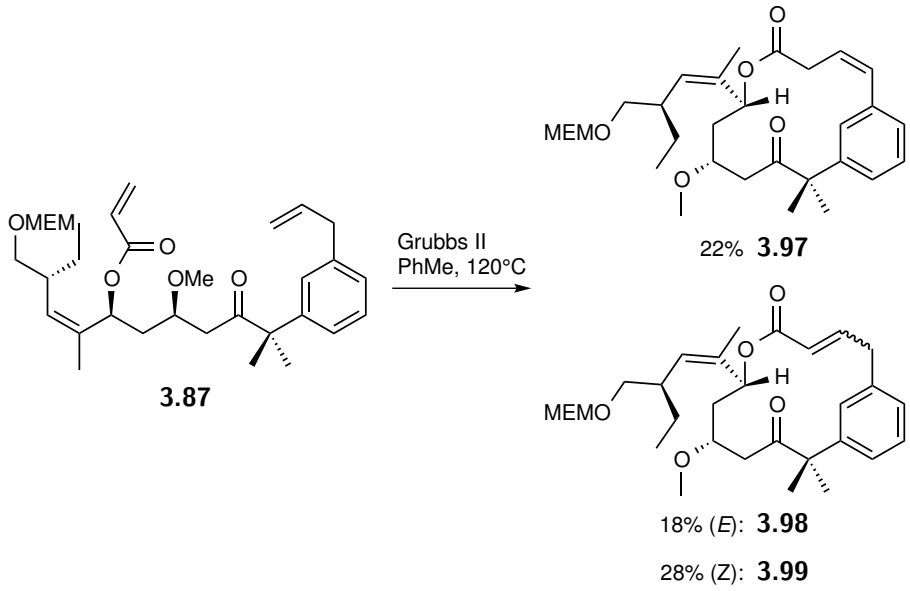
R_f: 0.15 (hexane/EtOAc 8/2)

HR-MS: calculated for ($M+NH_4^+$) 562.3738, found 562.3728 (Δ 1.9 ppm)

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.26 (app. t, J = 7.7 Hz, 1H), 7.10-7.06 (m, 2H), 7.03 (app. t, J = 2.0 Hz, 1H), 6.30 (dd, J = 17.3, 1.5 Hz, 1H), 6.01 (dd, J = 17.3, 10.4 Hz, 1H), 5.93 (dddd, J = 13.3, 10.9, 9.4, 6.6 Hz, 1H), 5.75 (dd, J = 10.4, 1.6 Hz, 1H), 5.75 (dd, J = 7.8, 5.9 Hz, 1H), 5.13 (app. dd, J = 10.2, 1.5 Hz, 1H), 5.09-5.03 (m, 2H), 4.65 (app. s, 2H), 3.69-3.60 (m, 3H), 3.55-3.52 (m, 2H), 3.45 (dd, J = 9.5, 5.6 Hz, 1H), 3.40 (dd, J = 9.5, 6.1 Hz, 1H), 3.38 (s, 3H), 3.38-3.35 (m, 2H), 3.13 (s, 3H), 2.68-2.60 (m, 1H), 2.55 (dd, J = 17.2, 6.1 Hz, 1H), 2.23 (dd, J = 17.2, 6.2 Hz, 1H), 1.82 (ddd, J = 14.4, 7.6, 7.0 Hz, 1H), 1.70 (d, J = 1.5 Hz, 3H), 1.61 (ddd, J = 14.4, 5.9, 4.8 Hz, 1H), 1.57-1.50 (m, 1H), 1.47 (s, 3H), 1.45 (s, 3H), 1.27-1.17 (m, 1H), 0.82 (app. t, J = 7.5 Hz, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 211.31 (C), 165.01 (C), 143.82 (C), 140.64 (C), 137.32 (CH), 133.81 (C), 131.99 (CH), 130.35 (CH2), 129.00 (CH), 128.95 (CH), 127.38 (CH), 126.65 (CH), 124.03 (CH), 116.17 (CH_2), 95.62 (CH_2), 74.47 (CH), 71.97 (CH_2), 70.68 (CH_2), 70.16 (CH), 66.71 (CH_2), 59.12 (CH_3), 56.46 (CH_3), 52.53 (C), 41.75 (CH_2), 40.41 (CH_2), 39.33 (CH), 37.09 (CH_2), 25.39 (CH_3), 25.10 (CH_2), 24.87 (CH_3), 18.60 (CH_3), 11.76 (CH_3)

5.12.5 Synthesis of macrolactone 3.98



In a flask fitted with a reflux condenser, containing **3.87** (17.2 mg, 32 μmol, 1 eq.) in toluene (31.6 ml ml) was added Grubbs 2nd generation catalyst (2.7 mg, 3.2 μmol, 0.1 eq.) at 110°C. After 15 min, the reaction mixture was poured in water (20 ml), the phases were separated and the aqueous phase was extracted with Et_2O (3 x 30 ml), dried over $MgSO_4$ and concentrated. Purification by means of consecutive flash column chromatography (hexane/acetone 8/2, CH_2Cl_2/Et_2O 98/2) provided **3.98** (3 mg, 18%) as a colorless oil, together with **3.99** (4.5 mg, 28%) and **3.97** (3.5 mg, 22%).

Formula: $C_{30}H_{44}O_7$

Molecular weight: 516.7 g/mol

HR-MS: calculated for ($M+NH_4^+$) 534.3425, found 534.3412 (Δ 2.6 ppm)

Most apolar compound 3.99

Name: (1'*Z*,3*Z*,3'*R*,4*S*,7*R*,9*S*)-11-oxo-7-[3'-(2"-methoxyethoxymethoxymethyl)-1'-methylpent-1'-enyl]-9-methoxy-12,12-dimethyl-6-oxabicyclo[11.3.1]hepta-

deca-1(17),3,13,15-quadruplen-5-one

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.24 (app.t, J = 7.7 Hz, 1H), 7.21 (app.t, J = 1.8 Hz, 1H), 7.15 (ddd, J = 7.8, 1.9, 1.2 Hz, 1H), 7.06 (app. d, J = 7.6 Hz, 1H), 6.51 (ddd, J = 11.6, 8.9, 7.8 Hz, 1H), 5.87 (dd, J = 11.5, 1.9 Hz, 1H), 5.78 (dd, J = 9.9, 2.1 Hz, 1H), 5.99 (dq, J = 10.3, 1.5 Hz, 1H), 4.69 (app. s, 2H), 4.25 (ddd, J = 14.2, 7.7, 2.0 Hz, 1H), 3.73-3.64 (m, 2H), 3.58-3.55 (m, 2H), 3.49-3.35 (m, 4H), 3.40 (s, 3H), 3.18 (s, 3H), 2.73-2.65 (m, 1H), 2.65 (dd, J = 16.8, 8.8 Hz, 1H), 2.14 (dd, J = 16.8, 4.1 Hz, 1H), 1.97 (ddd, J = 15.1, 9.9, 3.0 Hz, 1H), 1.67 (d, J = 1.5 Hz, 3H), 1.66 (ddd, J = 15.1, 6.5, 2.1 Hz, 1H), 1.61-1.55 (m, 1H), 1.58 (s, 3H), 1.45 (s, 3H), 1.23-1.13 (m, 1H), 0.82 (app. t, J = 7.5 Hz, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 210.98 (C), 165.11 (C), 144.02 (CH), 143.73 (C), 140.23 (C), 135.13 (C), 130.26 (CH), 128.87 (CH), 127.54 (CH), 127.29 (CH), 123.81 (CH), 123.28 (CH), 95.66 (CH_2), 74.41 (CH), 72.00 (CH_2), 71.02 (CH_2), 67.91 (CH), 66.74 (CH_2), 59.15 (CH_3), 56.87 (CH_3), 52.23 (C), 41.16 (CH_2), 39.46 (CH), 35.67 (CH_2), 33.26 (CH_2), 25.21 (CH_2), 25.13 (CH_3), 24.72 (CH_3), 18.52 (CH_3), 11.83 (CH_3)

Middle compound 3.97

Name: (1'*Z*,2*Z*,3'*R*,4*S*,7*R*,9*S*)-11-oxo-7-[3'-(2"-methoxyethoxymethoxymethyl)-1'-methylpent-1'-enyl]-9-methoxy-12,12-dimethyl-6-oxabicyclo[11.3.1]heptadeca-1(17),2,13,15-quadruplen-5-one

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.30 (app. t, J = 7.7 Hz, 1H), 7.26-7.21 (m, 2H), 7.01 (ddd, J = 7.4, 2.2, 1.2 Hz, 1H), 6.88 (d, J = 11.0 Hz, 1H), 5.88 (app. dt, J = 10.9, 8.1 Hz, 1H), 5.84 (dd, J = 9.8, 1.3 Hz, 1H), 5.03 (app. dd, J = 10.3, 1.4 Hz, 1H), 4.712 (d, J = 6.8 Hz, 1H, Apart of AB-spinsystem), 4.706 (d, J = 6.8 Hz, 1H, B part of AB-spinsystem), 3.77-3.67 (m, 3H), 3.59-3.55 (m, 2H), 3.54 (dd, J = 9.4, 4.8 Hz, 1H), 3.43-3.38 (m, 1H), 3.40 (s, 3H), 3.23 (s, 3H), 2.92-2.88 (m, 2H), 2.84 (dd, J = 17.1, 9.3 Hz,

1H), 2.78-2.69 (m, 1H), 1.92 (dd, J = 17.2, 4.1 Hz, 1H), 1.89 (ddd, J = 15.3, 5.3, 2.2 Hz, 1H), 1.81 (ddd, J = 15.4, 5.1, 1.5 Hz, 1H), 1.65-1.55 (m, 1H), 1.61 (d, J = 1.5 Hz, 3H), 1.54 (s, 3H), 1.49 (s, 3H), 1.25-1.15 (m, 1H), 0.83 (app. t, J = 7.5 Hz, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 211.57 (C), 170.44 (C), 144.00 (C), 138.06 (C), 134.93 (CH), 134.82 (C), 130.10 (CH), 128.81 (CH), 127.76 (CH), 126.67 (CH), 125.27 (CH), 124.28 (CH), 95.74 (CH_2), 74.55 (CH), 72.01 (CH_2), 70.86 (CH_2), 68.72 (CH), 66.79 (CH_2), 59.16 (CH_3), 57.25 (CH_3), 52.22 (C), 41.64 (CH_2), 39.40 (CH), 34.75 (CH_2), 34.01 (CH_2), 25.22 (CH_3), 25.18 (CH_2), 24.58 (CH_3), 18.42 (CH_3), 11.83 (CH_3)

Most polar compound 3.98

Name: (1'*Z*,3*E*,3'*R*,4*S*,7*R*,9*S*)-11-oxo-7-[3'-(2"-meth-oxyethoxymethoxymethyl)-1'-methylpent-1'-enyl]-9-methoxy-12,12-dimethyl-6-oxabicyclo[11.3.1]hepta-deca-1(17),3,13,15-quadruplen-5-one

^{1}H-NMR (500 MHz; $CDCl_3$): δ (ppm) = 7.27-7.23 (m, 2H), 7.17 (ddd, J = 8.0, 2.0, 1.2 Hz, 1H), 7.11 (app. dt, J = 7.4, 1.3 Hz, 1H), 6.85 (ddd, J = 15.9, 9.4, 4.8 Hz, 1H), 5.69 (ddd, J = 15.9, 1.9, 0.8 Hz, 1H), 5.68 (dd, J = 10.7, 1.8 Hz, 1H), 5.05 (app. dd, J = 10.5, 1.6 Hz, 1H), 4.72 (d, J = 6.6 Hz, 1H, A part of AB-spinsystem), 4.71 (d, J = 6.6 Hz, 1H, B part of AB-spinsystem), 3.89 (s, 3H), 3.26 (s, 3H), 2.83 (dd, J = 18.0, 9.5 Hz, 1H), 2.76-2.68 (m, 1H), 1.91 (ddd, J = 15.3, 6.2, 2.1 Hz, 1H), 1.80 (ddd, J = 15.4, 10.5, 1.6 Hz, 1H), 1.80 (dd, J = 18.0, 2.4 Hz, 1H), 1.64 (d, J = 1.5 Hz, 3H), 1.64-1.57 (m, 1H), 1.53 (s, 3H), 1.50 (s, 3H), 1.25-1.16 (m, 1H), 0.84 (app. t, J = 7.5 Hz, 3H)

APT (125 MHz; $CDCl_3$): δ (ppm) = 210.89 (C), 165.04 (C), 148.65 (CH), 143.83 (C), 139.62 (C), 134.91 (C), 131.08 (CH), 129.86 (CH), 129.11 (CH), 127.54 (CH), 124.45 (CH), 123.76 (CH), 95.83 (CH_2), 73.97 (CH), 72.06 (CH_2), 70.92 (CH_2), 69.71 (CH), 66.89 (CH_2), 59.10 (CH_3), 57.45 (CH_3), 53.32

(C), 43.88 (CH_2), 39.70 (CH), 37.85 (CH_2), 35.38 (CH_2), 25.27 (CH_2), 25.13 (CH_3), 24.32 (CH_3), 18.84 (CH_3), 11.89 (CH_3)

6

Nederlandse samenvatting

(+)-Peloruside A (**6.1**, figuur 6.1) is een natuurproduct dat cytotoxische activiteit vertoont bij nanomolaire concentratie.[52,75] Belangrijker echter, is dat het werkt als microtubuli-stabiliserend middel op dezelfde manier als paclitaxel, één van de belangrijkste hedendaagse chemotherapeutica.[82] Peloruside werd enkel gevonden op enkele specifieke plaatsen in Nieuw-Zeeland, en kan niet geoogst worden uit het gecultiveerd producerend organisme. Dit lage natuurlijk voorkomen gecombineerd met de complexitieit zorgt er voor dat het niet als dusdanig als medicijn kan dienen. Analyse van de structuur-activiteitsrelatie kan in dat geval gebruikt worden om vereenvoudigde analogen te ontwerpen die niet inboeten aan activiteit, en op die manier het volle potentieel van het natuurproduct uit te buiten.

Daarom werden in deze thesis enerzijds inspanningen geleverd om het belang van de substituenten op de pyranosering van peloruside na te gaan. Dit werd gedaan aan de hand van synthese van tetrahydropyranyl-analogen **6.2**, via de relatief onbekende Mukaiyama aldol - Prins reactie.[99]

Anderzijds werd een nieuwe synthese ontwikkeld voor een in ons lab eerder gesynthetiseerd analoog, pelofen (**6.3**, figuur 6.1) waarin de pyranosering van peloruside vervangen is door een fenylring.[149,150] Deze nieuwe synthese moest ons in staat stellen op een laat stadium kleine veranderingen toe te passen, en zo meer te weten te komen over de SAR van dit vereenvoudigd analoog en bij uitbreiding peloruside.

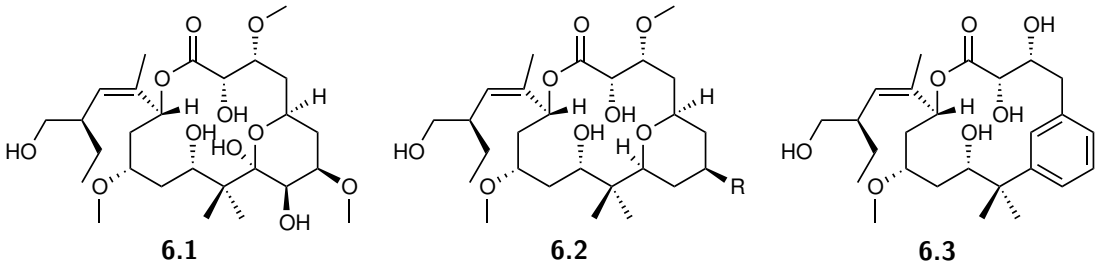
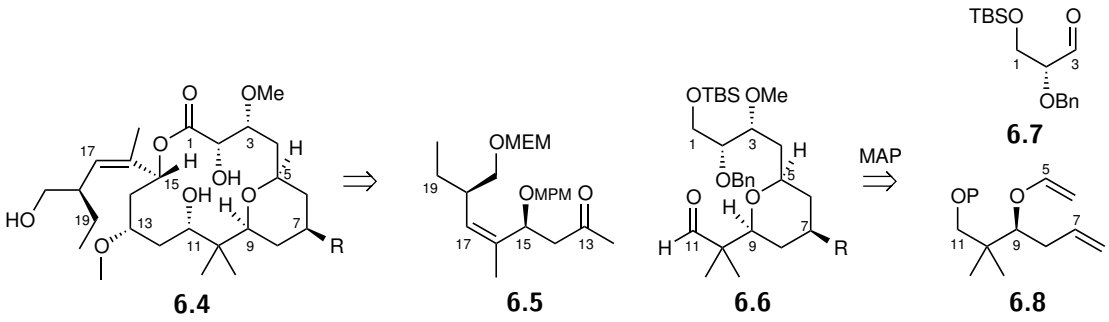


Figure 6.1

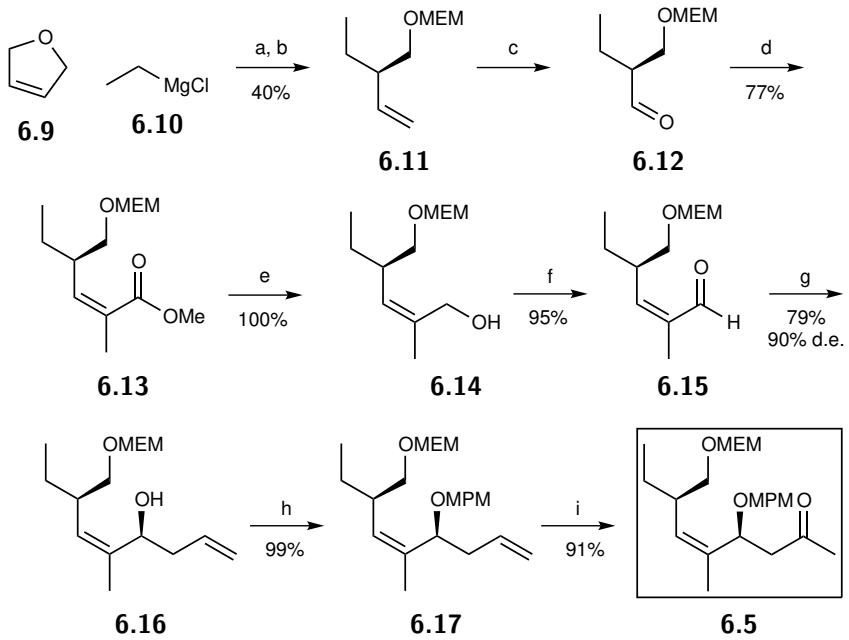
6.1 Tetrahydropyranyl analogen

The synthese van de tetrahydropyranyl-analogen (**6.4**, schema 6.1) is gebaseerd op de aldolkoppeling van twee geavanceerde intermediairen: een methylketon **6.5**, dat twee stereocentra en de dubbele binding van de zijketen bevat en een aldehyde **6.6**, dat de THP-ring en twee bijkomende stereocentra bevat. Voor de synthese van laatstgenoemd fragment werd beroept op de Mukaiyama aldol-Prins (MAP) reactie, een cascadereactie tussen een aldehyde **6.7** en een dubbel nucleofiel **6.8**, in aanwezigheid van een Lewiszuur.



Scheme 6.1: Retrosynthese van de beoogde THP-analogen

De synthese van het $C_{12}-C_{20}$ fragment **6.5** (schema 6.2) startte met de carbomagnesatie van dihydrofuran (**6.9**) met ethylmagnesium chloride (**6.10**), in een reactie die gekatalyseerd wordt door zirconium, en doorgaat met excellente controle over de enantioselectiviteit (>98:2).[101] Het resulterende homoallylisch alcohol werd beschermd als MEM-acetaal en de dubbele binding werd ge-ozonolyseerd, wat het aldehyde **6.12** opleverde. De *Z*-dubbele binding werd gevormd door middel van fosfonaat **6.18** in een modificatie van de Horner-Wadsworth-Emmons reactie, ontwikkeld door Still en Gennari.[104] De geometrie van de dubbele binding werd bevestigd door middel van NOE NMR spectroscopie. Een reductie tot het alcohol, gevolgd door oxidatie resulteerde in aldehyde **6.15** hetwelke diastereoselectief geallyleerd werd volgens Brown, met behulp van di-isopinocamfeylboraan.[206] Dit gebeurde zowel met een redelijk goed rendement (79%) als diastereomere overmaat (90%). De stereochemie van het gevormde carbinol werd aangetoond aan de hand



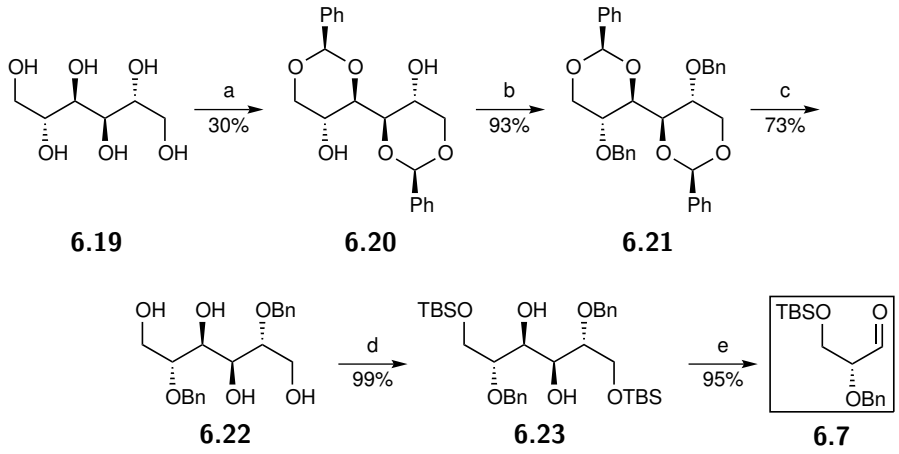
a) [(*S,S*)-ethylene-bis(4,5,6,7-tetrahydro-1-indenyl)]Zr(IV)BINOL , THF, 40h, RT; b) DIPEA, MEM-Cl, CH_2Cl_2, reflux; c) [i] O_3, CH_2Cl_2, -78°C; [ii] Ph_3P, CH_2Cl_2; d) 18-crown-6, KHMDS, THF, -78°C, $(CF_3CH_2O)_2POCH(CH_3)CO_2CH_3$; e) DIBAL-H, CH_2Cl_2, -78°C, 1h; f) DMP, pyridine, CH_2Cl_2, 1h, rt; g) [i] (-)-Ipc_2BOMe, allylMgBr, Et_2O, -78°C; [ii] NaOH, H_2O_2, RT; h) [i] NaH, THF, 0°C; [ii] MPM-Cl, TBAI, DMF, RT; i) $PdCl_2$, $Cu(OAc)_2.H_2O$, DMF:H_2O 9:1, O_2, RT

Scheme 6.2: Synthese van het C_{12}-C_{20} fragment

van Mosher-ester analyse.[207] Na bescherming van het homoallylisch alcohol **6.16** als MPM-ether, werd het eindstandig alkeen selectief omgezet tot methylketon **6.5** door gebruik te maken van een palladium-gekatalyseerde Wacker oxidatie.

Deze bouwsteen werd gesynthetiseerd in een lineaire sequentie van negen stappen met een totaalrendement van 21%. Dit rendement is vooral te wijten aan de eerste stap (carbomagnesatie) (40%) die werd geoptimaliseerd in termen van katalysator *turnover* nummer.

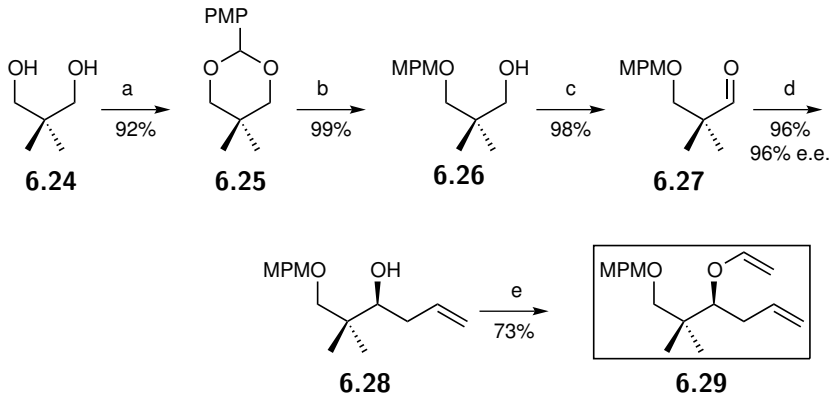
Het tweede fragment **6.6** is zelf opgebouwd uit twee bouwstenen (schema 6.1). De eerste hiervan, aldehyde **6.7**, werd gesynthetiseerd, startend van D-mannitol, waarvan vier hydroxyls beschermd werden met benzaldehyde als bis-1,3-4,6 benzylideen acetaal (**6.20**) met 30% rendement (schema 6.3). De overblijvende alcoholen werden gebenzyleerd, waarna de benzylideen acetalen opnieuw afgesplitst



a) PhCHO, H_2SO_4, DMF, RT; b) KOH, DMSO, BnBr, RT c) HCl, MeOH/C_6H_{14} 5/3, RT; d) TBSCl, imidazole, CH_2Cl_2, RT; e) $NaIO_4$, THF/H_2O 4/1, RT

Scheme 6.3: Synthese van aldehyde **6.7**

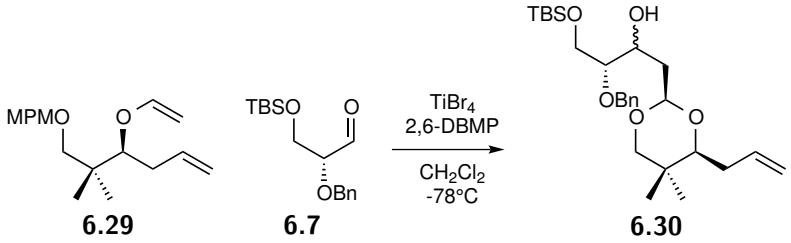
werden, om te komen tot tetra-alcohol **6.22**. Hiervan werden de primaire alcoholen beschermd als silylethers, resulterend in bis-silyl ether **6.23**. Oxidatieve splitsing van het overblijvend diol gebeurde met natriumperiodaat in water en leverde aldehyde **6.7** op in 19% rendement over 5 stappen.



a) 4-MeO-PhCH$(OMe)_2$, CSA, CH_2Cl_2, RT; b) $LiAlH_4$, $AlCl_3$, Et_2O, -10°C; c) [i] $(COCl)_2$, DMSO, -78°C [ii] Et_3N, CH_2Cl_2, -78°C; d) $[Ir(cod)Cl]_2$, (*S*)-(-)-Cl, MeO-BIPHEP, Cs_2CO_3, 4-Cl-3-NO_2-benzoic acid, THF, allylOAc, 2-PrOH, 120°C; e) $Hg(CF_3COO)_2$, $EtOCHCH_2$, RT

Scheme 6.4: Synthese van bisnucleofiel **6.29**

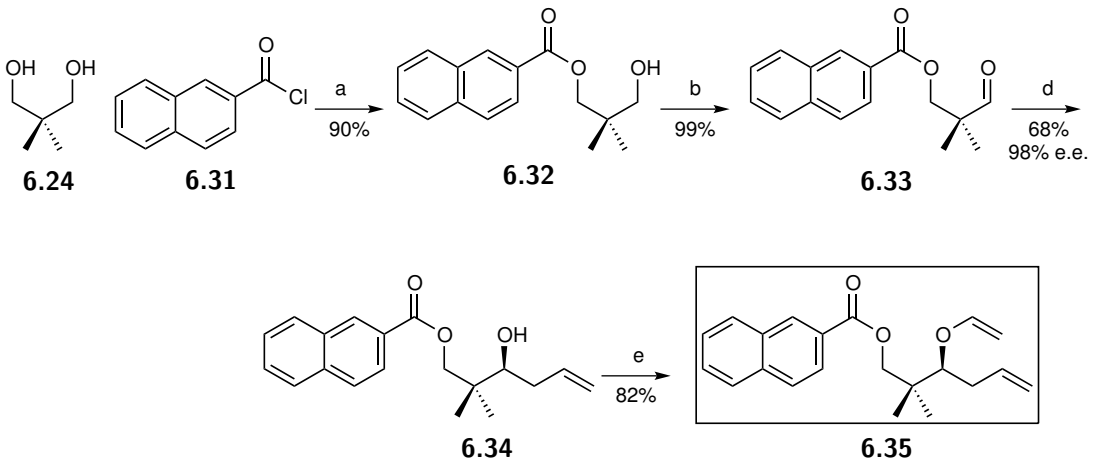
De tweede bouwsteen voor de opbouw van het C_1-C_{11}-fragment startte met de acetalisering van 2,2-dimethyl-1,3-propaandiol met 4-methoxybenzyl dimethylacetaal, gevolgd door reductieve splitsing tot alcohol **6.26** (schema 6.4). Dit werd geoxideerd onder invloed van Swern condities, resulterend in aldehyde **6.27**, hetwelke stereoselectief geallyleerd werd met behulp van een chirale iridium-katalysator bij hoge temperaturen.[132] Het resulterend homoallylisch alcohol **6.28** werd omgevormd tot de vinylether door middel van een kwik-gekatalyseerde reactie, resulterend in de vorming van het bisnucleofiel **6.29**[136] Het totaalrendement voor deze bouwsteen bedroeg 62% over 5 stappen en de enantiomere overmaat bedroeg 96%.



Scheme 6.5: Eerste poging tot de Mukaiyama aldol - Prins reactie

Uit een eerste poging om de Mukaiyma aldol-Prins reactie tussen aldehyde **6.7** en enol ether **6.29** te bewerkstelligen, bleek dat de 4-methoxyfenylmethyl ether (MPM) niet bestand was tegen de Lewis-zure condities die gebruikt werden voor de cyclizatie (schema 6.5). Bijgevolg kon enkel acetaal **6.30** geïsoleerd worden, en werd het bisnucleofiel opnieuw gesynthetiseerd, ditmaal gebruik makend van een minder electronenduwende beschermende groep, namelijk een naftoyl ester.

De synthese van de naftoyl-beschermde enol ether **6.35** startte met de enkelvoudige bescherming van diol **6.24** met naftoylchloride (schema 6.6). Swern oxidation van het resulterende alcohol in **6.32** leverde aldehyde **6.33** op, dat dan opnieuw geallyleerd werd, gebruik makend van de eerder toegepaste Krische-condities. Het resulterende homoallylic alcohol **6.34** werd gevormd met een geisoleerd rendement van 68% en een enantiomere overmaat van 98%. De laatste kwik-gekatalyseerde vinylvorming gebeurde met een rendement van 82%. Globaal gezien, werd deze tweede generatie enol ether gesynthetiseerd in 4 stappen met een totaalrendement

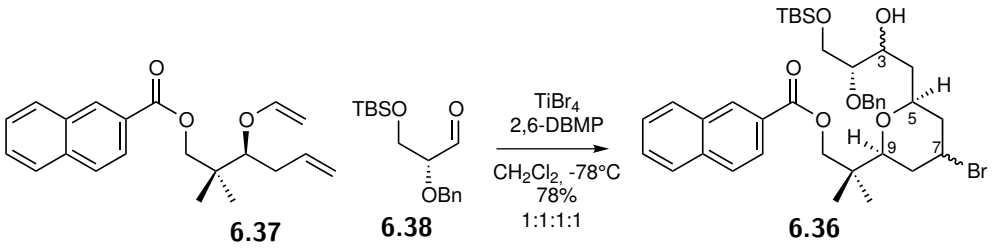


a) DMAP, NEt_3, CH_2Cl_2, RT; b) [i] $(COCl)_2$, DMSO, -78°C [ii] Et_3N, CH_2Cl_2, -78°C; c) $[Ir(cod)Cl]_2$, (*S*)-(-)-Cl, MeO-BIPHEP, Cs_2CO_3, 4-Cl-3-NO_2-benzoic acid, THF, allylOAc, 120°C; d) $[Ir(cod)Cl]_2$, (*S*)-(-)-Cl, MeO-BIPHEP, Cs_2CO_3, 4-Cl-3-NO_2-benzoic acid, THF, allylOAc, 2-PrOH, 120°C; e) $Hg(CF_3COO)_2$, $EtOCHCH_2$, RT

Scheme 6.6: Synthese van de ester beschermde C_4-C_{11} enol ether **6.35**

van 50% en met een excellente optische zuiverheid.

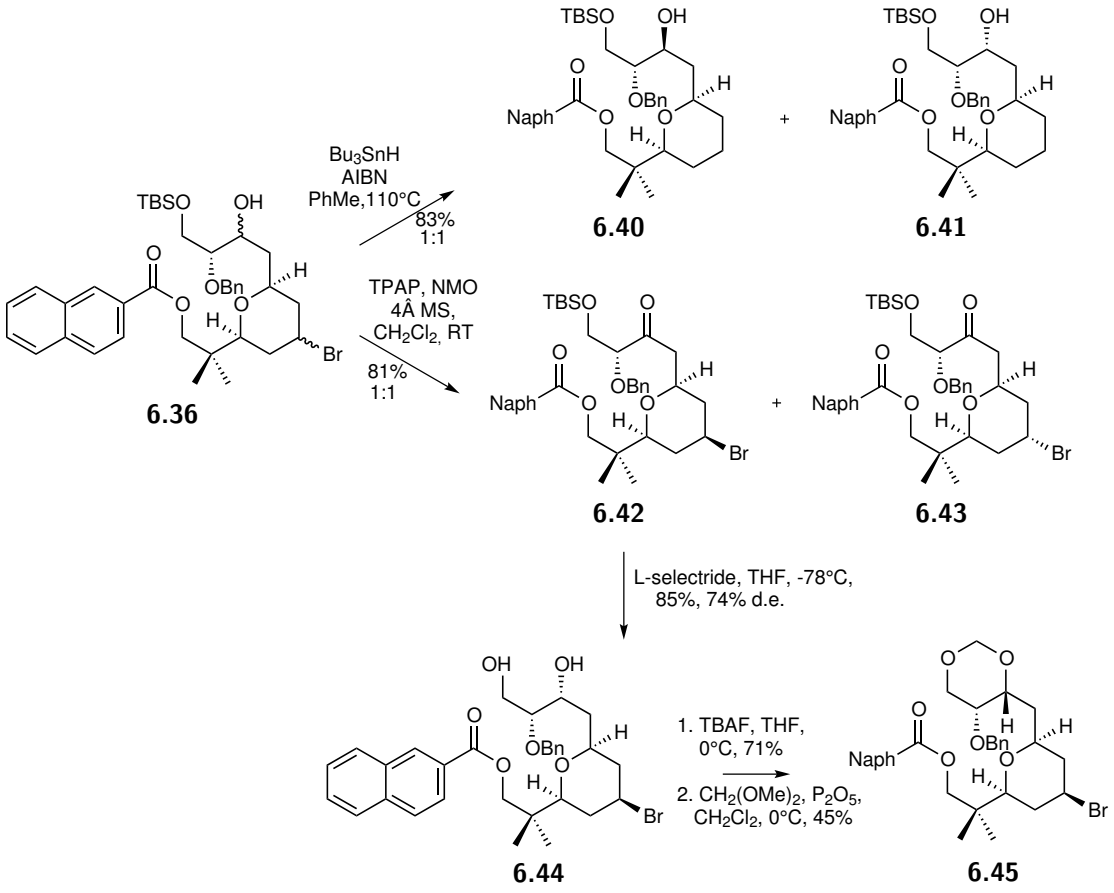
De tweede poging tot de Mukaiyama aldol - Prins reactie was succesvol in die zin dat het volledige koolstofskelet gevormd werd in een behoorlijk rendement van 78% (schema 6.7). Helaas was de reactie minder succesvol in termen van diastereoselectiviteit: de beoogde bromo-tetrahydropyran ether **6.36** werd gevormd als mengsel van diastereomere alcoholen op de C_3 positie en als mengsel van axiaal en equatoriaal bromide op de C_7 positie, in equimolaire hoeveelheden.



Scheme 6.7: Mukaiyama aldol - Prins reactie met bisnucleofiel **6.39**

Verschillende pogingen werden ondernomen om de diastereoselectiviteit op te

krikken: andere Lewiszuren werden gebruikt, de volgorde van toevoegen werd aangepast, de temperatuur werd beter gecontroleerd, ... Helaas resulteerden deze pogingen niet in een verbetering van de diastereomere overmaat. Het opdrijven van de omvang van het aldehyde door de TBDMS-ether te vervangen door een minder zuurgevoelige TBDPS-ether, resulteerde niet in een verbetering in diastereomere selectiviteit, maar verhoogde het rendement tot 84%.



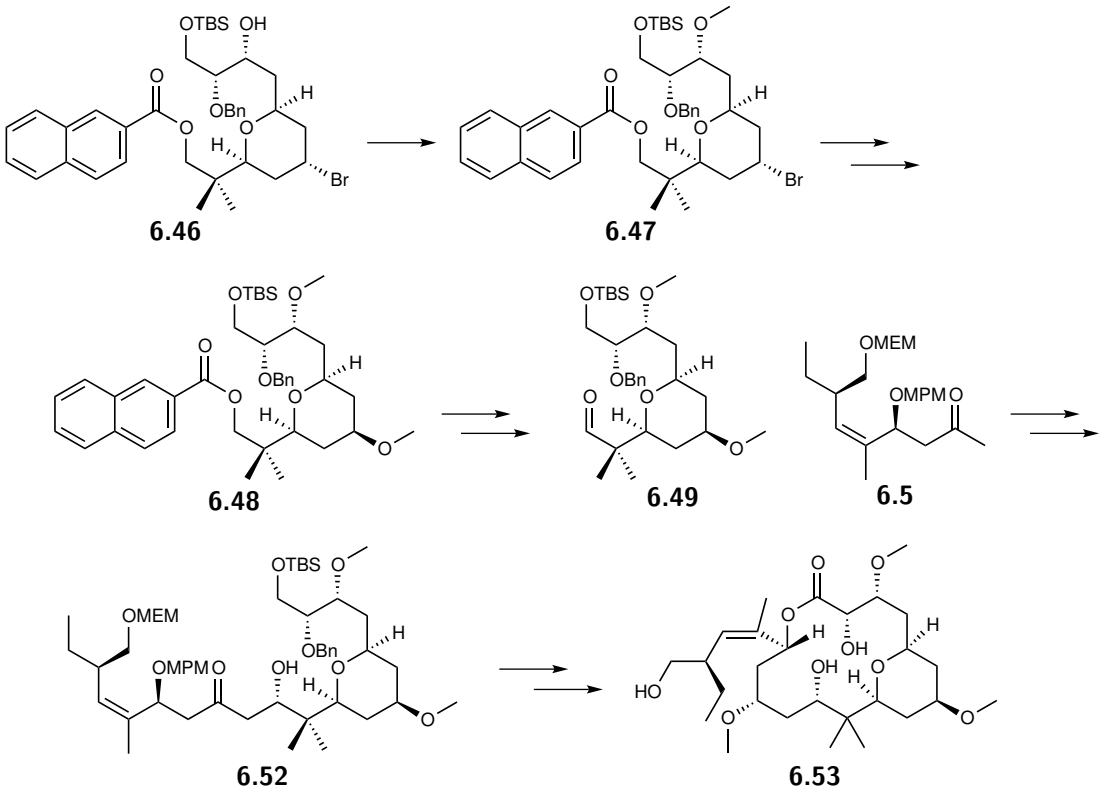
Scheme 6.8: Verdere synthese van het MAP-product **2.89**

Omdat de analytische methoden niet toereikend waren, werd het complexe mengsel van diastereomeren geanalyseerd aan de hand van chemische modificatie (schema 6.8). Reductieve verwijdering van het bromide leverde een scheidbaar mengsel van diastereomere C_3-alcoholen (**6.40** en **6.41**) op, terwijl oxidatie van de

C_3-alcoholen een scheidbaar mengsel van equatoriaal **6.42** en axiaal **6.43** bromide opleverden. De stereochemie van de C_5-substituent was altijd *cis* in vergelijking met de substituent op C_9, waarvan de stereochemie eerder werd aangetoond na de allylering.

Na de chromatografische scheiding werd keton **6.42** stereoselectief gereduceerd met lithium selectride met vorming van alcohol **6.44** in 85% rendement, nu aangerijkt in één diastereomeer. De configuratie van dit alcohol werd aangetoond door de TBS-ether te ontschermen en een acetaal te vormen (**6.45**) tussen de alcoholen op C_1 en C_3. Uit de Karplus vergelijking kon afgeleid worden dat het nieuw gevormde carbinol centrum *cis* staat ten opzichte van de benzyloxy groep, waarvan de stereochemie vaststaat, aangezien deze voortkomt uit de *chiral pool*.

Op dit ogenblik werd de focus van dit doctoraat bijgesteld naar de synthese van fenyl-analogen. Verdere belangrijke stappen voor het vervolg van dit eerste deel zijn (schema 6.9): de methylering van het C_3-alcohol van **6.46**, en transformatie van het bromide **6.47** naar bijvoorbeeld methylether **6.48**. Na ontscherming van de naftoyl ester, moet het primaire alcohol geoxideerd worden naar aldehyde **6.49**, wat dan gekoppeld kan worden met het $C_{12}-C_{20}$ fragment **6.5** tot **6.50**. Daarna is er nog een stereoselectieve reductie nodig om het koolstofskelet met de juiste stereochemie te vervolledigen. Na selectieve methylering,[57] oxidatie en ontscherming zou dan het ω-hydroxyzuur gevormd worden, wat nodig is voor de macrolactonisatie. Eindontscherming zou dan resulteren in het 8,9-dehydroxy analoog **6.51** van peloruside.

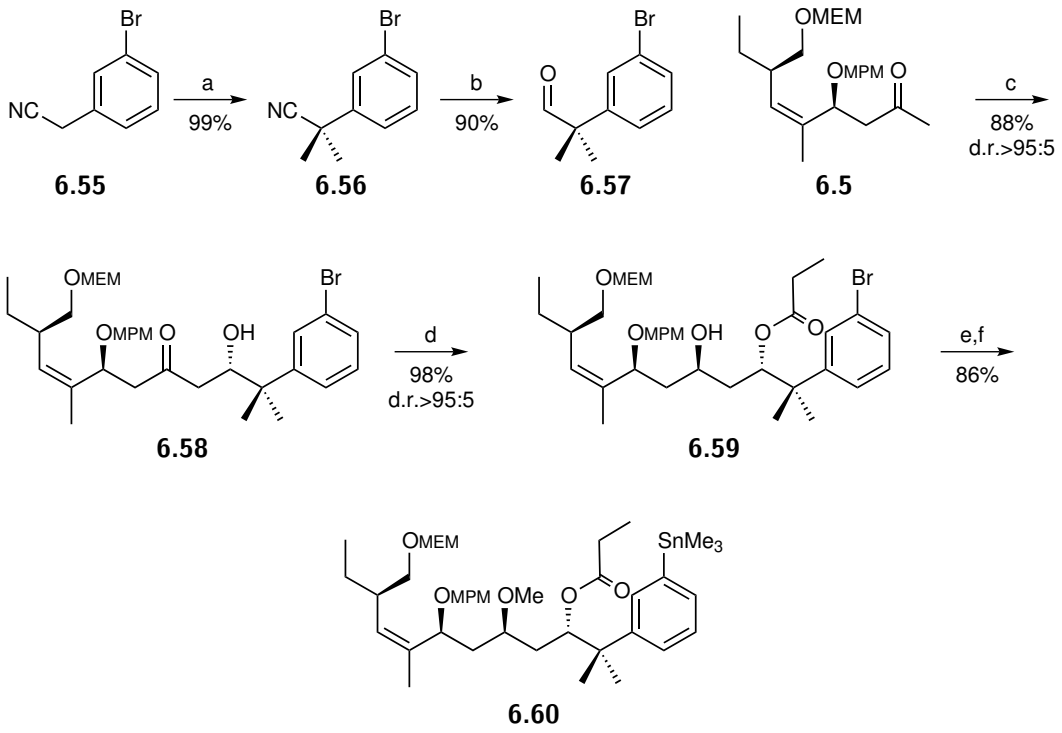


Scheme 6.9: Toekomstige stappen ter vervollediging van de synthese van het 8,9-dehydroxy analoog van (+)-Peloruside A (**6.54**).

6.2 Fenyl analogen

6.2.1 Pelofen B *via* macrolactonisering

Voor pelofen B **6.3** (figuur 6.1) werd een verbeterde synthese ontwikkeld, startend van het commercieel beschikbare 3-bromofenyl acetonitrile **6.55**, hetwelke eerst gealkyleerd werd tot **6.56** (scheme 6.10). Dit werd gereduceerd tot het imine, wat na zure hydrolyse aldehyde **6.57** opleverde, met 89% rendement over 2 stappen. Het $C_{12}-C_{20}$ methylketone dat eerder gesynthetiseerd was (**6.5**) kon dan gebruikt worden in een stereoselectieve aldolreactie onder invloed van dicyclohexylboor chloride, resulterend in β-hydroxyketon **6.58** in 88% rendement, als een enkel diastereomeer.[153]



a) KO*t*Bu, MeI, THF, -40°C; b) [i] DIBAH, PhMe, -78°C, [ii] aq. 6M HCl, RT; c) [i] $(Cy)_2BCl$, NEt_3, Et_2O, -78°C; [ii] MeOH, pH 7 buffer, H_2O_2, RT; d) EtCHO, SmI_2, THF, -20°C; e) Me_3OBF_4, 1,8-bis(dimethylamino)naphtalene, CH_2Cl_2, RT; f) $Me_3SnSnMe_3$, $Pd(PPh_3)_4$, PPh_3, PhMe, 70°C

Scheme 6.10: Synthese van het C_5-C_{20} fragment in de vernieuwde synthese van pelofen.

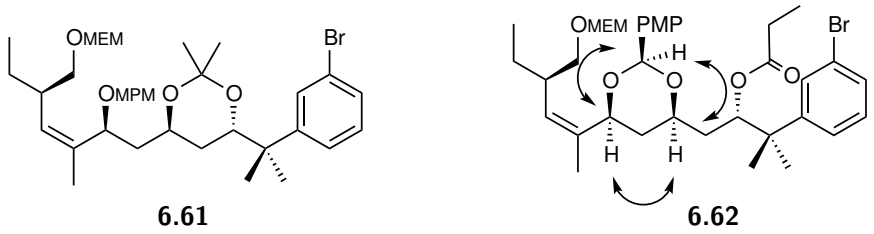
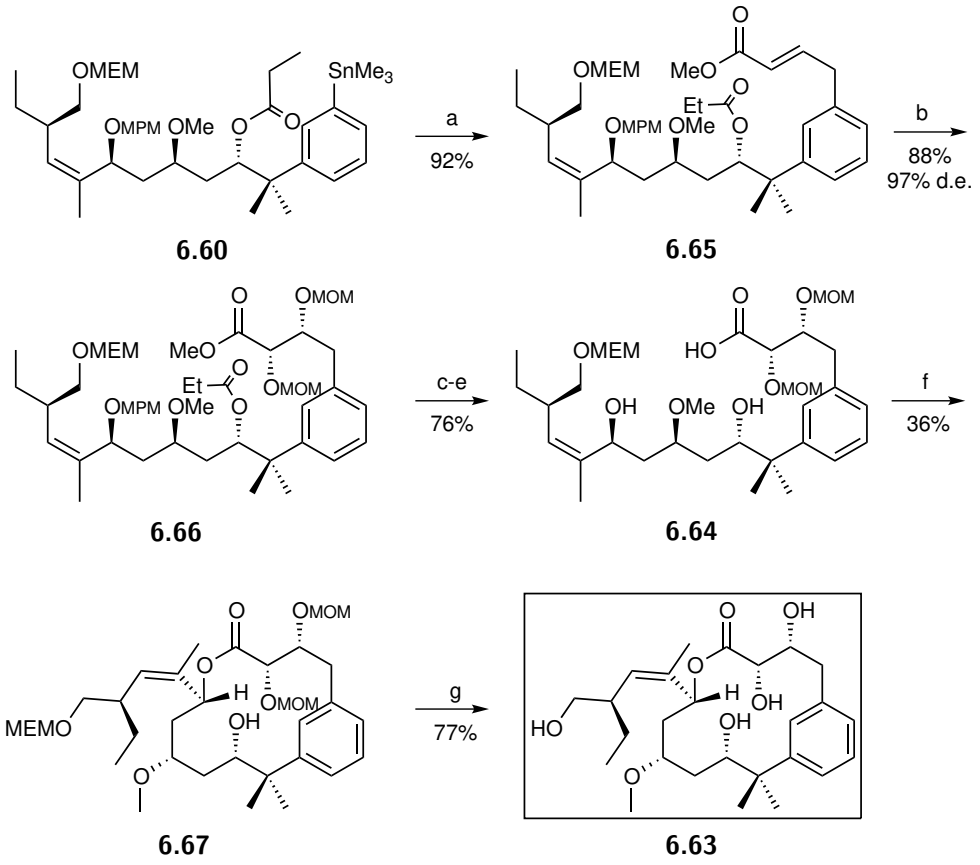


Figure 6.2

Op dit stadium werd de absolute stereochemie toegewezen via Mosher-ester synthese en analyse. In een volgende stap werd gebruik gemaakt van propionaldehyde en samarium dijodide in een Evans-Tishchenko reductie.[165] Dit zorgde voor differentiatie ten opzichte van een diol, waarbij een alcohol nu ester beschermd is (**6.59**). Op dit stadium, werd ook de relatieve stereochemie tussen het alcohol dat gegenereerd werd tijdens de aldolreactie (C_{11}) en het alcohol dat gegenereerd werd in de Evans-Tishchenko reductie (C_{13}) aangetoond, door de synthese van een acetonide (**6.61**, figuur 6.2), gevolgd door NMR-analyse. Ook werd de relatieve stereochemie tussen het MPM-beschermd alcohol (C_{15}) en het alcohol dat gevormd werd tijdens de reductie aangetoond door de synthese van het corresponderende PMP-acetaal (**6.62**, figuur 6.2) en opnieuw NMR-analyse. Na methylering van het nieuw gevormde alcohol in **6.59**, werd het arylisch bromide omgezet in het trimethyltin derivaat **3.9** door middel van een palladium(0)-gekatalyseerde Stille koppeling.

Voor de vervollediging van het koolstofskelet van het fenylanaloog **6.63** werd het geavanceerd stannaan **6.60** gekoppeld met het commercieel beschikbare methyl 4-bromocrotonaat in een tweede Stille koppeling (scheme 6.11). Gebruik makend van AD-mix β, werd de dihydroxylering van het olefine voltooid met een diastereomere overmaat van 97% en een rendement van 88%. Vervolgens werden beide alcoholen beschermd als MOM-ethers met een rendement van 97%, en werd het MPM beschermd alcohol selectief vrijgesteld met DDQ (95%).

De bedoeling was dan om beide resterende esters tegelijk te hydrolyseren onder basische omstandigheden. Hierbij gaf het gebruik van LiOH de minste nevenproducten, maar de reactie duurde lang (meerdere dagen). Uiteindelijk werd het γ-hydroxyzuur (**6.64**) gevormd met 83% rendement na 7 dagen zonder volledige conversie bereikt te hebben.

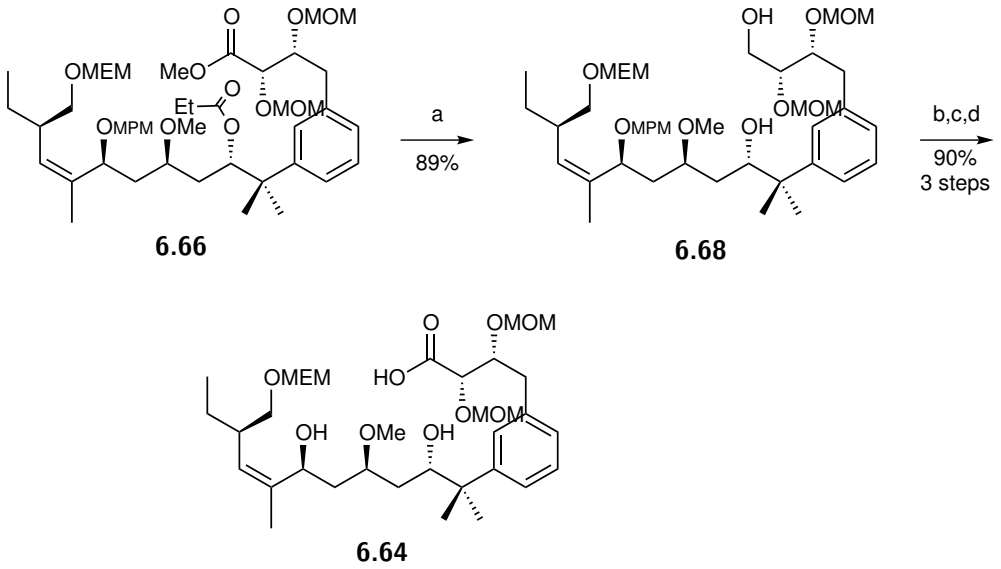


a) (*E*)-4-Br-$CH_2CHCHCOOMe$, $Pd_2dba_3.CHCl_3$, THF, 70°C; b) AD-mix β, $MeSO_2NH_2$, $NaHCO_3$, *t*BuOH:H_2O 1:1, RT; c) MOM-Cl, DIPEA, CH_2Cl_2, reflux; d) DDQ, pH7 buffer, CH_2Cl_2, RT; e) LiOH.H_2O, THF:H_2O 3:1, RT; f) [i] 2,4,6-trichlorobenzoylchloride, DIPEA, THF, RT; [ii] DMAP, PhMe, RT; g) 4M HCl, THF:H_2O 1:1, RT

Scheme 6.11: Vervolledigingen van de synthese van pelofen.

Om de lange reactietijd te omzeilen, werd een andere tactiek toegepast: beide esters werden reduceerd met $LiALH_4$, terwijl de MPM ether nog intact was (scheme 6.12). Het resulterende primaire alcohol werd dan selectief geoxideerd tot het carbonzuur, via het aldehyde. Daarna werd de MPM-ether afgesplitst in bijzijn van het carbonzuur, met een rendement van 80% over vier stappen.

Voor de macrolactonisering werden verschillende condities getest, maar het oorspronkelijke rendement van 36%, onder Yamaguchi-Yonemitsu condities. Zowel variatie in condities als activatiereagens, vertoonden geen verbetering in rende-



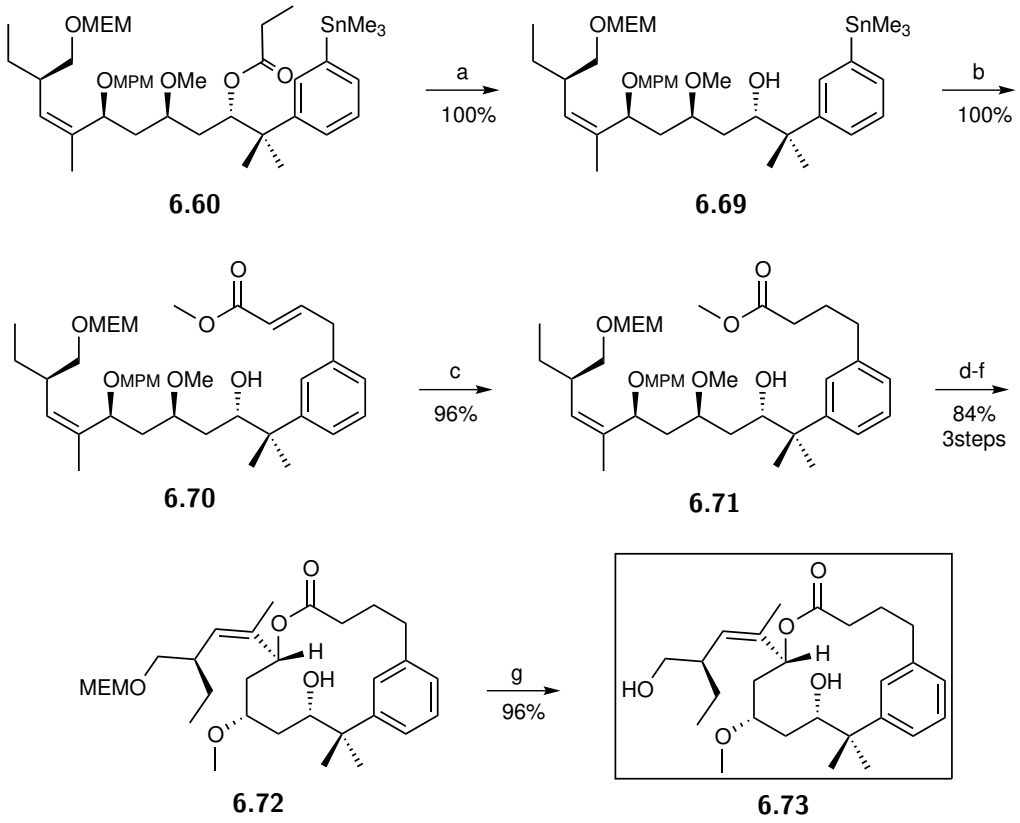
a) $LiAlH_4$, Et_2O, 0°C; b) TEMPO, $PhI(OAc)_2$, CH_2Cl_2,RT; c) NaH_2PO_4, $NaClO_2$, 2-Me-2-butene, tBuOH:H_2O 1:1, RT; d) DDQ, pH 7 buffer, CH_2Cl_2, RT

Scheme 6.12: Alternatieve synthese van het ω-hydroxyzuur **6.64**.

ment. De eindontscherming onder zure omstandigheden resulteerde in het fenylanaloog **6.63** met 77% rendement.

Globaal gezien werd de synthese van het fenylanaloog vervolledigd in 22 stappen, in een langste lineaire sequentie van 20 stappen, startend van ethylmagnesiumchloride, met een totaalrendement van 2.7%. Dit is lineair 1 stap minder dan de oorspronkelijke synthese, 4 stappen minder wat betreft het totaal aantal stappen en een verbetering in totaalrendement met ongeveer 400% (0.7% totaalrendement in de originele route).

6.2.2 Synthese van 2,3-dideoxy pelofen (6.73)



a) $LiAlH_4$, Et_2O, 0°C; b) (*E*)-4-Br-$CH_2CHCHCOOMe$, $Pd_2dba_3.CHCl_3$, THF, 70°C; c) $NiCl_2.6H_2O$, $NaBH_4$, MeOH, 0°C; d) DDQ, pH7 buffer, CH_2Cl_2, RT; e) $LiOH.H_2O$ THF:H_2O 1:1 RT; f) [i] 2,4,6-trichlorobenzoylchloride, DIPEA, PhMe, RT; [ii] DMAP, PhMe, RT; g) *n*-BuSH, $ZnBr_2$, CH_2Cl_2, RT

Scheme 6.13: Synthese van het 2,3-dideoxy analoog van pelofen (**6.73**).

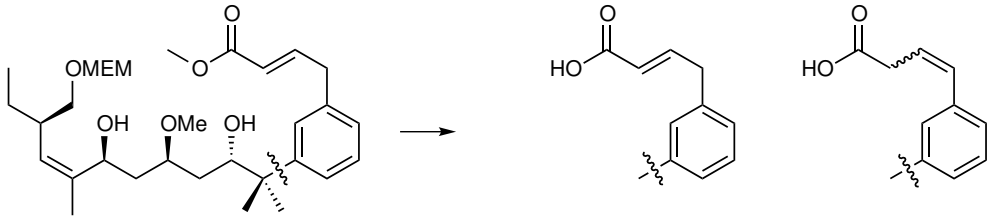
Een analoog van pelofen, waarin de substituenten op de C_2 en C_3 positie ontbreken, kan informatie verschaffen over het belang van deze hydroxylgroepen voor de activiteit. Dit 2,3-dideoxy analoog was relatief eenvoudig toegankelijk via de hierboven beschreven route. (schema 6.13).

Startend van stannaan **6.60** werd het probleem van de moeilijke ontscherming van de propionaatester ontweken door deze eerst te reduceren. Het resulterend alcohol **6.69** vereiste geen beschermende groep voor de volgende stappen. De Stille-koppeling met het voorheen gebruikte 4-bromocrotonaat, resulteerde in on-

verzadigd ester **6.70**. Hiervan werd de dubbele binding van het onverzadigd ester uitgereduceerd door middel van nikkel-katalyse, zonder de dubbele binding in de zijketen aan te tasten, wat ester **6.71** opleverde met 96% rendement over drie stappen. Na ontscherming van de MPM-ether en basische hydrolyse van de methylester, was het resulterende hydroxycarbonzuur klaar voor macrolactonisering. Deze ging in dit geval uitzonderlijk goed: toepassen van de standaard Yamaguchi condities, resulteerde in het macrolacton **6.72** met een rendement van 84% over drie stappen. The eindontscherming, gebruik makend van een thiol als scavenger in combinatie met een Lewiszuur, resulteerde in het 2,3-dideoxy analoog **6.73** in 96% rendement.

Globaal gezien werd dit analoog bekomen na 20 stappen, startend van ethylmagnesiumchloride, met een totaal aantal stappen van 22 en een totaalrendement van 12%. Helaas zijn er nog geen significante resultaten betreffende de activiteit beschikbaar.

6.2.3 Nieuwe route naar pelofen B en toegang tot analogen op de C_2-C_3-positie



Scheme 6.14: Geobserveerde isomerisatie tijdens de verzeping van **6.74**.

Aangezien de macrolactonisering van het ongesubstitueerd analoog zeer vlot doorging, werden pogingen ondernomen om de ringsluiting te vervolledigen terwijl de dubbele binding op de C_2-C_3-positie nog aanwezig was. Deze aanpak zou ons in staat gesteld hebben om substituenten in te voeren op een zeer laat stadium

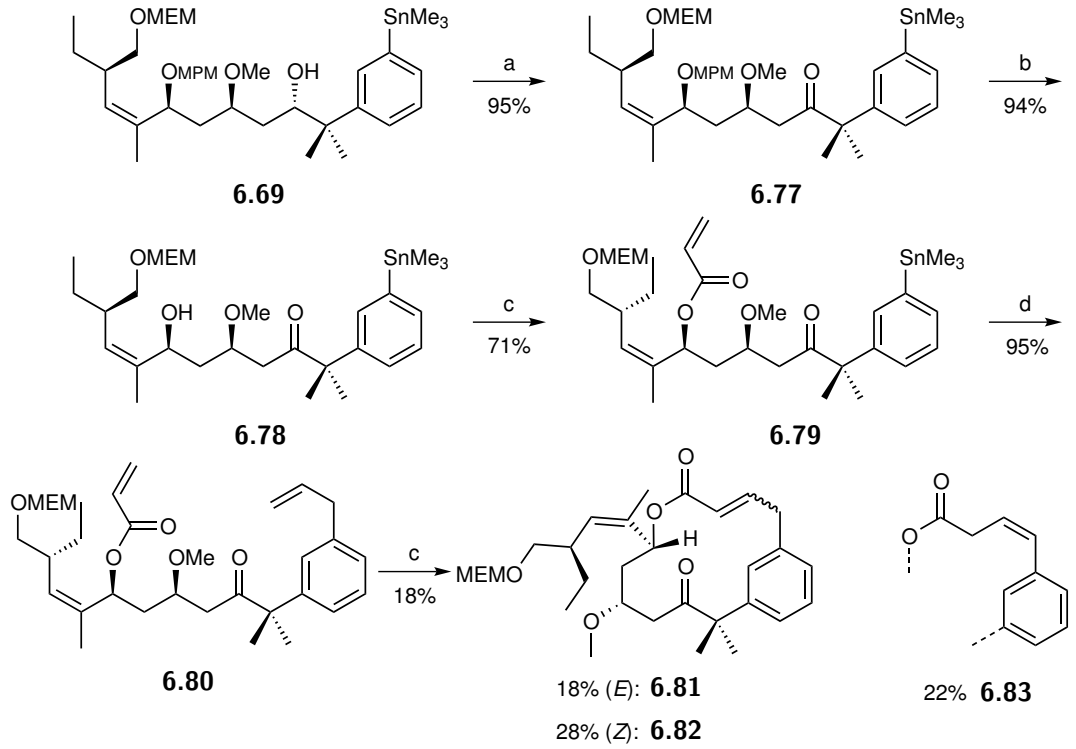
in de synthese, wat ideaal zou zijn, aangezien van een gemeenschappelijke precursor snel analogen te ontwikkelen zijn. Helaas werd tijdens de verzeping van de geconjugeerde methylester **6.74** slechts een kleine hoeveelheid van het beoogde carbonzuur **6.75** gevormd, en er was duidelijk vorming van de styreen-derivaten **6.76**, door isomerisatie van de dubbele binding. Een mogelijke oplossing van dit probleem, koppeling van het 4-bromocrotonzuur bleek ineffectief aangezien dezelfde isomerisatie werd geobserveerd onder de basische omstandigheden die gebruikt werden bij de macrolactonisering. Omwille van de complexiteit van de gevormde reactiemengsels werd deze route niet verdergezet.

6.2.4 Pelofen B via ringsluitingsmetathese

De laatste manier om tot pelofen B te komen die in deze thesis gevalideerd werd, was gebaseerd op de ringsluitingsmetathese. Naast de macrolactonisering, is dit een veel voorkomende manier om macrolactonen van grotere omvang te synthetiseren.[198]

Aangezien de selectieve acrylering van het alcohol op de C_{15} positie voor problemen zorgde, werd besloten om het concurrerende alcohol op de C_{11} positie te oxideren naar het keton, alvorens het allylisch alcohol op C_{15} vrij te stellen (schema 6.15). Deze manier van bescherming zou ons in staat gesteld hebben om later zowel het vereiste als het geinverteerde alcohol te vormen, terwijl ook andere substituenten nog steeds tot de mogelijkheden zouden behoren. De oxidatie gebeurde door gebruik te maken van Ley's condities en leverde keton **6.77** in 95%. Vervolgens werd de MPM-ether verwijderd, waardoor het allylisch alcohol **6.78** vrijgesteld werd. De geoptimaliseerde condities voor de acryloylering maakten gebruik van een 0.1M oplossing van acryloylchloride in CH_2Cl_2 en DIPEA en resulteerden in acryloylester **6.79** in 71%, met nog 10% uitgangsproduct resterend.

The laatste stap in de synthese van het precursor dieen **6.80** was de allylering van de aromaat onder Stille condities, die nu uitgevoerd werd in puur allylbromide, met een rendement van 95%, zonder observatie van isomerisatie van de dubbele binding.



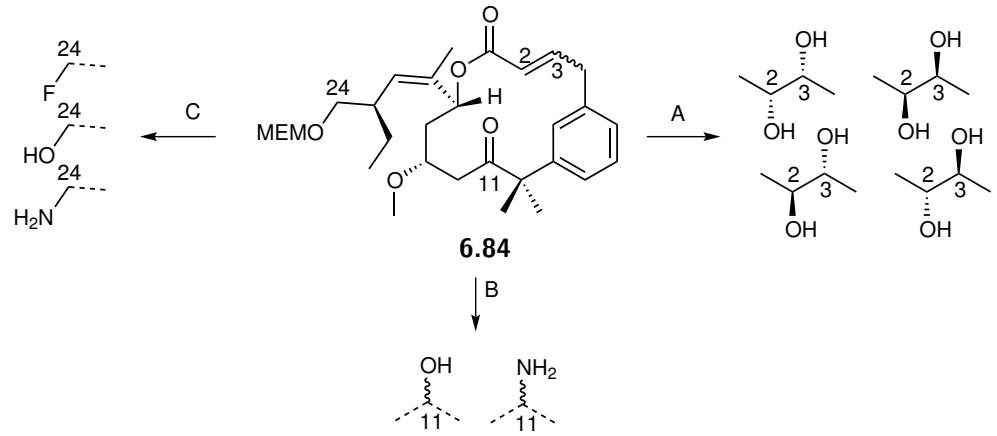
a) TPAP, NMO, 4Â molecular sieves, CH_2Cl_2,RT; b) DDQ, pH7 buffer, CH_2Cl_2, 0°C; c) $CH_2CHCOCl$, DIPEA, CH_2Cl_2, RT, 0°C; d) CH_2CHCH_2Br, $Pd_2dba_3.CHCl_3$, 60°C; e) Grubbs II, PhMe, 110°C

Scheme 6.15: Synthese van het onverzadigd macrolacton **6.81** door ringsluitingsmetathese

De ringsluitingsmetathese zelf werd geoptimaliseerd in termen van monomeer- versus oligomeervorming, in functie van verdunningsgraad, solvent, katalysator, reactietijd en temperatuur. Door gebruik te maken van Grubbs' tweede generatie katalysator bij 110°C in tolueen, werd een geoptimaliseerde ratio van 70:30 ten voordele van het monomeer, bekomen na enkele minuten. Zoals verwacht werd een mengsel van *E* en *Z*-olefine gevormd. Tijdens de opschaling van deze reactie daarentegen, werd waargenomen dat de 66% geïsoleerd ringproduct was samengesteld uit drie fracties: de *E*-en *Z*-isomeren van de ringgesloten geconjugeerde ester (18% **6.81** vs. 28% **6.82**, respectievelijk) maar ook het *Z*-styreenproduct (22% **6.83**).

6.2.5 Besluit en toekomstperspectieven

Tijdens dit onderzoek werd de synthese van het fenylanaloog van peloruside (pelofen B) geoptimaliseerd voor alle stappen behalve de macrolactonisering. Een factor die niet onderzocht werd bij deze reactie, is de invloed van de temperatuur. Afgaande op de goede resultaten die behaald werden bij de ringsluitingsreactie bij hogere temperaturen, zou dit een mogelijkheid kunnen bieden voor de verdere optimalisatie.



Scheme 6.16: Snelle toegang tot analogen van pelofen door diversificatie van **6.85**

Voor de snelle introductie van modificatie op een later stadium in de synthese, lijkt de ringsluitingsmethode de betere aanpak. Startend van de onverzadigde macroring **6.84**, zijn verscheidene analogen toegangelijk door eenvoudige synthesestappen (schema 6.16). Op de C_2-C_3-positie kan dhydroxylering van de *E*-dubbele binding toegang geven tot de *syn*-alcoholen, terwijl dihydroxylering van de *Z*-dubbele binding kan resulteren in de *anti*-diolen (stap A). Reductie van het keton op de C11-positie kan resulteren in beide epimere alcoholen, waar reductieve aminering de epimere amines oplevert (stap B). Het primair alcohol op positie C_{24} kan eenvoudig ontschermd worden onder zure omstandigheden, zodat het substituties kan ondergaan (stap C).

List of Abbreviations

Å: Ångström

Ac: acetyl

AD: asymmetric dihydroxylation

AIBN: azobisbutyronitrile

APC: anaphase promoting complex

APT: attached proton test

BAIB: bisacetoxy iodobenzene

BINOL: 1,1'-bi-2-naphtolate

BIOS: biology oriented synthesis

Bn: benzyl

Boc: *tert*-butyl oxycarbonyl

BPS: *tert*-butyl diphenylsilyl

Bz: benzoyl

CBS: Corey Bakshi Shibata

CDK: cyclin dependent protein kinase

COSY: correlation spectroscopy

d: doublet

DBMP: di-*tert*-butyl 4-methylpyridine

DDQ: 2,3-dichloro-5,6-dicyanobenzoquinone

d.e.: diastereomeric excess

DHQD: dihydroquinidine

DIBAH: diisobutylaluminiumhydride

DIPEA: N,N-diisopropylethylamine

DMF: N,N-dimethylformamide

DMAP: 4-dimethylaminopyridine

DMP: Dess-Martin periodinane

DMSO: dimethylsulfoxide

DNA: deoxyribo nucleic acid

DOS: diversity oriented synthesis

DTBP: di-*tert*-butylpyridine

EDCI: 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide

e.e.: enantiomeric excess

EI-MS: electron impact ionization-mass spectrometry

EMA: European Medicine Agency

ESI: electrospray ionization

Et: ethyl

FDA: United States Food and Drug Administration

FOS: function oriented synthesis

GC: gas chromatography

GDP: guanosine 5'-diphosphate

GTP: guanosine 5'-triphosphate

HATR: horizontal attenuated total reflection

HDX: hydrogen/deuterium exchange

HMBC: heteronuclear multiple bond correlation spectroscopy

HMDS: hexamethyldisilazane

HSQC: heteronuclear single quantum correlation spectroscopy

HTS: high-throuhput screening

HWE: Horner-Wadsworth-Emmons

Hz: hertz

Ipc: isopinocampheyl

***i*Pr:** *iso*-propyl

IR: infrared

KHMDS: potassium hexamethyldisilazide

LC: liquid chromatography

LLS: longest linear sequence

m: multiplet (NMR); medium (IR)

MAP: Mukaiyama aldol - Prins

MDA: microtubule destabilizing agent

MDR: multi drug resistence

Me: methyl

MEM: (2'-methoxyethoxy)-methyl

MHz: megahertz

M.M.: molar mass

MOM: methoxymethyl

MPM: 4-(methoxyphenyl)-methyl

MS: mass spectrometry

MSA: microtubule stabilizing agent

MT: microtubule

MTT: 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

MTPA: α-methoxy-α-trifluoromethylphenylacetyl

NCE: new chemical entity

nM: nanomolar

NMR: nuclear magnetic resonance

NOE: nuclear Overhauser effect

NOESY: nuclear Overhauser effect spectroscopy

Pgp: permeability glycoprotein

PKC: protein kinase C

Ph: phenyl

PHAL: phtalazine

PMB: *para*-methoxybenzyl

PMP: *para*-methoxyphenyl

Pr: propyl

PTK-2: protein tyrosine kinase 2

q: quadruplet

R&D: Research and Development

R_f: ratio to front

RCM: ring closing metathesis

s: singlet (NMR); strong (IR)

SEM: trimethylsilyl ethoxymethyl

SRB: sulforhodamine B

t: triplet

T: Tesla

TBAI: tetrabutylammonium iodide

TBDPS: *tert*-butyl diphenylsilyl

TBS: *tert*-butyl trimethylsilyl

Tf: triflate (trifluoromethyl sulphonate)

TFA: trifluoroacetic acid

THF: tetrahydrofuran

THP: tetrahydropyran

TLC: thin layer chromatography

***tert*:** tertiary

TES: triethylsilyl

TIPS: triisopropylsilyl

TMS: trimethylsilyl

TOCSY: total correlation spectroscopy

TTS: transition state

w: weak (IR)

WHO: World Health Organization

Xc: chiral auxiliary

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